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BACTERIOLOGIC INVESTIGATIONS ON THE BLOOD, SYNOVIAL FLUID AND SUBCUTANEOUS NODULES IN RHEUMATOID (CHRONIC INFECTIOUS) ARTHRITIS *

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The clinical evidence pointing to an infective origin of rheumatoid arthritis has led numerous investigators to seek a bacterial agent to which etiologic significance could be ascribed. A wide variety of such agents has been reported by various workers at various times, but the lack of uniformity in the results obtained has served to confuse rather than to clarify the issue. In recent years the widespread interest in rheumatoid arthritis and the recognition of the social and economic importance of this disease have stimulated renewed activity in the search for the etiologic agent.

HISTORICAL

Bacteriologic studies on the blood and tissues in rheumatoid arthritis are so numerous that a complete review of the results obtained is not within the scope of this report. Moreover, a critical review of the literature is difficult, for numerous investigators have presented the results obtained without reference to the technic employed, the kind of cases investigated or the methods adopted for the identification of the organisms found. Extensive reviews [1] of the literature have recently appeared, from which the résumé presented in table 1 has been abstracted. The

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* The Arthritis Clinic of the Presbyterian Hospital has adopted the classification and nomenclature for rheumatic diseases provisionally recommended by the British Ministry of Health and the International League for the Control of Rheumatism. In this classification the term "rheumatoid arthritis" is used to designate that form of chronic multiple arthritis more commonly called "chronic infectious" or "atrophic" in America.

1. Pathogenic Streptococci, Ann. Pickett-Thomson Research Lab. pt. 2, **4**:253 (April) 1929. Jordan, E. P.: Microbic Etiology of Rheumatic Fever and Arthritis, Arch. Path. **10**:79 (July) 1930.

TABLE 1.—*Results of Bacteriologic Study Recorded in the Literature*

Author	Year	Tissue Cultured	Number Cases	Results
Schüller	1892-1906	Synovial fluid and joint tissues	230	Gram-positive diplobacillus in 150 cases
Bannatyne, Wohlman and Blaxall	1896	Synovial fluid	18	Gram-negative diplobacillus (by smear) in all instances
Crawford and Mallim	1903	Synovial fluid	48	Majority sterile: few positive cultures considered accidental contamination
McCrae	1904	Synovial fluid	110	Negative
Davis	1912	1. Blood and synovial fluid	14	Negative
		2. Tonsillar crypts	42	Streptococcus hemolyticus 28
Rosenow	1914	Regional lymph glands	54	Streptococcus viridans 32
				Bacillus welchii 14
				Staphylococcus 5
				Diphtheroid bacillus 5
				Bacillus mucosus 3
				Micrococcus catarrhalis 1
				Gonococcus 1
				Sterile 7
Rowlands	1914-1915	Blood and synovial fluid	40	Negative
Moon and Edwards	1917	Blood and synovial fluid	83	Nonhemolytic streptococcus (other organisms occasionally found) 18
Richards	1920	1. Blood	104	Streptococcus viridans 14
		2. Synovial fluid	54	Streptococcus viridans 4
Munro	1922	Synovial fluid	50	Gram-positive coccus (with little hemolysis and little decoloration) 4
Billings, Coleman and Hibbs	1926	Joint tissue	14	Streptococcus viridans or nonhemolyticus 5
				Streptococcus hemolyticus 1
				Mixed 1
Hadjopoulos and Burbank	1927	Blood	145	Streptococcus hemolyticus 9
				Streptococcus viridans 6
				Diphtheroid bacillus 8
				Staphylococcus aureus 5
Suranyi and Forro	1928	Blood	25	Streptococcus viridans 19
Forkner, Shands and Posten	1928	1. Synovial fluid	63	Streptococcus viridans 11
				Gonococcus 2
				Staphylococcus aureus 1
		2. Regional lymph glands	21	Streptococcus viridans 9
				Gonococcus 1
Posten	1929	Regional lymph glands	120	Streptococcus viridans 67
				Streptococcus nonhemolyticus 2
				Staphylococcus aureus 2
				Gonococcus 1
Cecil, Nicholls and Stainsby	1929	Blood	78	Streptococci, (83%, "attenuated hemolytic") 48
Margolis and Dorsey	1930	Blood	89	169 blood cultures: (1) 68 following technic of Cecil, Nicholls and Stainsby:
				Streptococcus viridans 3
				Diphtheroid bacillus 2
				(2) 74 following authors' own technic:
				Streptococcus viridans 4
Nye and Waxelbaum	1930	1. Blood	21	Negative
		2. Synovial fluid and lymph glands	5	Inconsistent

results reported by Margolis and Dorsey [2] and by Nye and Waxelbaum [3] are included in the summary.

From table 1 it is apparent that there is no unanimity of opinion as to the specific etiology of rheumatoid arthritis. Three alternative explanations may be offered to account for the wide variety of findings recorded:

2. Margolis, H. M., and Dorsey, A. H. E.: Bacteriology of Blood in Chronic Infectious Arthritis, J. Infect. Dis. **46**:442 (June) 1930.

3. Nye, R. N., and Waxelbaum, R. A.: J. Exper. Med. **52**:885, 1930.

1. Rheumatoid arthritis may not be the result of infection by one particular bacterial agent but rather by a multiplicity of such agents.

2. The bacteria recovered may or may not be of etiologic significance, and, in either case, may represent only casual invasion of the blood stream and joint tissues from a distant focus.

3. The organisms recovered may not actually be present in the body fluids, but may be the result of contamination due to imperfect technic.

The remarkable results recently reported by Cecil, Nicholls and Stainsby [4] on the bacteriology of the blood and joints in rheumatoid arthritis are of particular interest. These authors, by the use of a special technic, claimed to have demonstrated the presence of streptococci in the blood stream in 61.5 per cent of a series of 78 patients examined. They reported that 83.3 per cent of the strains recovered are culturally and biologically identical and appear to be "attenuated hemolytic streptococci." They also reported that a streptococcus culturally and biologically identical with the strain isolated from the blood can sometimes be cultivated from one of the affected joints of the same patient.

Because of the unusual nature of this report and the importance of such an observation in the study of rheumatoid arthritis the present investigation was undertaken. A preliminary report of the results of this investigation has recently been presented.[5]

During this study all possible assistance was extended to us by Drs. Cecil, Nicholls and Stainsby. They permitted us to study the technic as carried out at Bellevue Hospital, and the early portion of the work was done in their laboratory. Broth was supplied by Dr. Nicholls for a portion of this investigation.

METHODS

The greatest care was exercised to follow the technic described by Cecil, Nicholls and Stainsby. This technic, as described in their original article,[4] is as follows:

> The technic employed for blood cultures was an adaptation of that recommended by Clawson in his blood culture studies of rheumatic fever.
>
> Twenty cubic centimeters of blood was taken aseptically from the arm with a Luer syringe, placed in two sterile culture tubes and allowed to clot. Each tube was treated separately in the following way:
>
> The tube was centrifugated, and all the serum drawn off with a sterile pipet. The clot was then broken up in the original culture tube with a sterile glass tube, ¼ inch (6.35 mm.) in diameter. The fragments of clot were drawn up in the same glass tube, and transferred to a 3 ounce bottle containing 50 cc. of beef heart infusion broth with a p_H of 7.6 (0.5 per cent sodium chloride, 1 per cent peptone).

4. Cecil, R. L.; Nicholls, E. E., and Stainsby, W. J.: Bacteriology of Blood and Joints in Chronic Infectious Arthritis, Arch. Int. Med. **43**:571 (May) 1929.

5. Dawson, M. H.; Olmstead, M., and Boots, R. H.: Proc. Soc. Exper. Biol. & Med. **28**:419, 1931.

The bottle was then put in the incubator at 37 C. and left there unopened for five days.

At the end of this time, a tube containing 8 cc. of a 1.5 per cent beef heart infusion agar was placed in the water bath and heated until the agar was completely melted. The tube was then partially cooled and 0.5 cc. of whole rabbit blood added to it. Finally, the tube was seeded with 0.1 cc. of broth from the original blood culture, and the contents poured into a petri dish. The culture was allowed to incubate for from twenty-four to forty-eight hours. Similar pour-plate cultures were made every three to five days thereafter until the original blood culture had been in incubation for thirty days. If, at the end of this time, the subcultures were still sterile, the sediment in the original blood culture bottle was drawn out with a sterile glass tube and centrifugated. After centrifugation, part of the sediment was examined by means of stained smears, while the remainder was cultured, part of it in fresh blood broth and part of it on blood agar plates. If these final cultures from the sediment showed no growth, the blood culture was considered sterile.

All of these cultures and transfers were made under a hood, in order to eliminate contaminations as far as possible. All contaminated cultures were discarded.

When colonies appeared on the plates, they were transferred into blood broth and identified by the usual bacteriologic methods.

Examination of this technic shows that the average number of manipulations involved in the procedure was as follows:

Taking of blood	1
Separation of clot	1
Centrifugation	1
Pipetting off serum	1
Breaking up clot and transferring to flask	1
Opening of flasks to obtain samples for plates	6
Centrifugation of sediment	1
Pipetting off supernatant fluid from sediment	1
Streaking plate from sediment	1
Making smear from sediment	1
Adding blood broth to sediment	1
Subculturing sediment cultures	2
Total number of manipulations	18

The second sample of blood was, as a rule, subjected to a smaller number of manipulations inasmuch as plates were not poured from it until cultures of the first sample either showed growth or remained sterile for the full period of thirty days. The average number of manipulations to which the second specimen was subjected was approximately 14.

These 14 to 18 manipulations, extending over a period of six weeks, constituted the average number to which all cultures were subjected. It is therefore not surprising that a considerable number of contaminations were encountered in the course of this study. The occurrence of all bacterial growth, including even the most obvious contamination, is recorded in the work herewith presented.

THE PRESENT STUDY

In the present investigation blood cultures were done only according to the technic described by Cecil, Nicholls and Stainsby. The relatively large amount of blood required and the intricacies of the procedure precluded a more extensive investigation by other cultural methods with other nutrient mediums. It is therefore emphasized that the conclusions drawn from this investigation apply only to the narrow range of cultural methods employed.

The type of patient selected presented a characteristic clinical syndrome with chronic polyarthritis, frequently accompanied by swelling and deformity of the joints affected. The great majority of cases chosen for study were in the active stage of the disease. Cases of osteoarthritis (hypertrophic, degenerative) were not included in the investigation. The study extended over a period of twelve months from March, 1929, to March, 1930. The possible effect of seasonal variations was therefore eliminated.

In the course of the investigation 105 separate blood cultures were done on 80 patients. In the majority of instances the specimens of blood obtained at each venipuncture were divided into two portions, so that in all 204 samples of blood were cultured. In 18 selected patients cultures were made on two occasions, in 3 on three occasions and in 1 on six occasions.

Control Material.—In order that correct conclusions might be drawn from the occurrence of bacterial growth in the blood cultures of arthritic patients, 31 samples of blood were obtained from 16 normal persons and subjected to similar methods of culture. By way of further interest, 16 tubes of sterile autoclaved agar were subjected to the same manipulations and cultured by the same technic as that described by Cecil, Nicholls and Stainsby.

The results of these investigations are presented in the following tables:

TABLE 2.—*Summary of Blood Cultures on Patients with Rheumatoid Arthritis*

Number of blood cultures		105
Number of samples of blood		204
Number of patients		80
Of the 204 samples of blood: 146 (72%) remained sterile; 58 (28%) yielded growth		
Organisms recovered:		
Gram-positive bacillus (coarse)	21	
Diphtheroid bacillus	13	
Staphylococcus	17	
Streptococcus viridans	2	
Streptococcus anhemolyticus	1	
Gram-positive coccus (exact nature undetermined)	2	
Mold	2	
	58	

In addition, colonies of bacteria occasionally appeared in the pour-plates, but their presence in the flask was not established. These colonies

were composed of a wide variety of organisms comparable to those recovered from the flasks. A few colonies of Streptococcus viridans and Streptococcus anhemolyticus appeared on three occasions.

Each specimen, on the average, was subjected to 15 manipulations, or 3,075 manipulations for the entire series.

Colonies of a variety of bacteria also occasionally appeared in the pour-plates, but their presence in the flask was not established.

Each sample, on the average, was subjected to 15 manipulations, or a total of 465 manipulations for the entire series.

In addition, one pour-plate showed 10 colonies of Streptococcus viridans, but subsequent platings from the same flask remained sterile.

Each specimen, on the average, was subjected to 18 manipulations or a total of 228 manipulations for the entire series.

TABLE 3.—*Summary of Blood Cultures on Control Subjects*

Number of blood cultures	16
Number of samples of blood	31
Number of subjects	15
Of the 31 samples of blood: 27 (87%) remained sterile; 4 (13%) yielded growth	
Organisms recovered:	
Gram-positive bacillus (coarse)	1
Diphtheroid bacillus	1
Staphylococcus	1
Mold	1
	4

TABLE 4.—*Summary of Cultures of Samples of Sterile Agar Subjected to Similar Manipulations*

Number of samples of sterile agar	16
Of the 16 samples: 12 (75%) remained sterile; 4 (25%) yielded growth	
Organisms recovered:	
Diphtheroid bacillus	2
Streptococcus viridans	1
Gram-positive coccus (coarse, air?)	1
	4

The results of (1) blood cultures on patients suffering from rheumatoid arthritis, (2) blood cultures on normal persons and (3) cultures of specimens of sterile agar subjected to similar manipulations, according to the technic of Cecil, Nicholls and Stainsby, have led to the following conclusions:

1. In spite of the greatest care to perform all manipulations under sterile precautions, the technic, in our experience, was so involved as to call into serious question the significance of all bacterial growth encountered.

2. Blood cultures on patients suffering from rheumatoid arthritis failed to yield results that could be considered of etiologic significance.

3. No essential difference was found in the bacteria encountered in the three groups of material cultured.

4. The appearance of typical Streptococcus viridans on two occasions during the culture of specimens of sterile agar, subjected to similar manipulations, was felt to be of significance.

JOINT CULTURES

While the scope of the present investigation was primarily confined to the study of blood cultures, the bacteriology of the synovial fluid of a number of patients suffering from rheumatoid arthritis was also investigated. In the majority of cases the synovial fluid was withdrawn from the knee joint, but occasionally a small amount was obtained by aspiration of the wrist joint, the ankle joint and the proximal interphalangeal joints of the fingers.

The synovial fluid was withdrawn under sterile precautions and cultured in a variety of mediums which included the following: blood broth, hormone broth, meat broth, dextrose ascitic broth, and dextrose ascitic agar shakes. The meat broth was heated in a water bath at 100 C. for twenty minutes and allowed to cool to body temperature before being inoculated. The cultures in the dextrose ascitic agar shakes were carried out under petrolatum seal. In some cases the amount of fluid available was insufficient for culture in all the mediums mentioned. In other cases, when more material was available, all the nutrient mediums named were employed and varying amounts of synovial fluid were cultured in the same medium. All the cultures were kept in the incubator at 37 C. for at least thirty days and carefully examined for the presence of bacterial growth at four or five day intervals during that time. This procedure greatly added to the number of manipulations and naturally increased the probability of contamination. In all, 23 samples of joint fluid, obtained from 19 patients, were examined by this technic, with the following results: gram-positive bacilli (coarse), 3; diphtheroid bacilli, 3, and staphylococci, 1.

Because of the variety and nature of the organisms encountered and because of the possibility of contamination in cultures subjected to repeated manipulations over such a prolonged period, it was felt that no etiologic significance could be attached to the results obtained.

CULTURES ON SUBCUTANEOUS NODULES

It has been pointed out in previous communications [6] that subcutaneous nodules are of not infrequent occurrence in patients suffering from rheumatoid arthritis. Such nodules were observed in 43 patients who presented themselves for treatment at the Arthritis Clinic of the

6. Dawson, M. H.; Sia, R. H. P., and Boots, R. H.: J. Lab. & Clin. Med. **15**:1065, 1930. Dawson, M. H., and Boots, R. H.: Subcutaneous Nodules in Rheumatoid (Chronic Infectious) Arthritis, J. A. M. A. **95**:1844 (Dec. 20) 1930.

Presbyterian Hospital during the past eighteen months. Sections were obtained on 16 of these nodules and the material was subjected to careful pathologic investigation. All the material examined showed a uniform and highly characteristic histologic structure.[7] For these reasons particular attention was directed toward the bacteriologic study of the subcutaneous lesions of this disease.

Sixteen nodules, obtained from 11 patients, were cultured in a variety of mediums which included the following: blood broth, meat broth and dextrose ascitic agar. Whenever sufficient material was available, cultures were carried out anaerobically as well as aerobically. All cultures were kept in the incubator at 37 C. for at least thirty days and carefully examined every few days for the occurrence of bacterial growth. The results of these cultures were as follows: diphtheroid bacilli, 3, and staphylococci, 2.

Sections of the subcutaneous nodules were stained by Gram's method and carefully examined for the presence of bacteria. In no case was it possible to demonstrate the occurrence of micro-organisms in the characteristic subcutaneous lesions of this disease.

For the same reasons as those enumerated in the case of the joint cultures, it was felt that no etiologic significance, other than that of a negative character, could be attached to the results obtained.

SUMMARY

1. One hundred and five blood cultures, the majority in duplicate, were carried out on 80 patients suffering from rheumatoid arthritis according to the technic of Cecil, Nicholls and Stainsby. As control material, 31 samples of blood from normal persons and 16 samples of sterile autoclaved agar were subjected to similar manipulations.

2. The blood cultures on patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance.

3. No significant difference was observed in the bacteria encountered in the blood cultures of patients and those observed during the culture of the control material under similar conditions.

4. Streptococcus viridans was occasionally encountered during the culture of the control material as well as during the culture of specimens of the patients' blood.

5. Aerobic and anaerobic cultures of 23 specimens of synovial fluid obtained from patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance.

6. Aerobic and anaerobic cultures of 12 subcutaneous nodules obtained from patients suffering from rheumatoid arthritis failed to yield organisms that could be considered of etiologic significance.

7. Dawson, M. H., and Pappenheimer, A. M.: Scient. Proc., Am. Soc. Path. & Bact., April, 1930.

BASAL METABOLISM

I. THE ERROR OF BASAL METABOLISM DETERMINATION AND THE NORMAL RANGE OF BASAL METABOLISM *

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The error of basal metabolism determination is of interest clinically chiefly as it affects the usefulness of basal metabolism determination as a diagnostic procedure. It may then be expedient to begin a study of this error with a consideration of the "normal range of basal metabolic rates," and to pass from this to a discussion of the error of determination and its implications.

For a proper evaluation of the "normal range of basal metabolic rates" it is necessary to know two things. The first is a measure of the central tendency of the metabolism of normal persons. This will be referred to in this paper as the "zero point." The second is a measure of the spread of the basal metabolism of normal persons about this "zero point"—a measure of the dispersion of the distribution. These factors will be discussed separately.

THE ZERO POINT

Every metabolism standard has a zero point. The most obvious solution of the quest for the zero point is to accept the zero point of the standard used as the true zero point. But when one realizes that the zero point of two different standards for adults may differ by as much as 9 per cent,[1] it becomes apparent that this cannot be generally satisfactory. The situation with regard to children's standards is considerably worse.

There are differences in the level of metabolism of groups of normal subjects reported by various investigators not explainable by chance but reflecting either real differences in the populations studied or differences in technic such as would result in finding rates consistently higher in one laboratory than in another. A discussion of which of these two explanations is the more likely is outside the scope of this article. *The point of importance is that such differences do exist, and that they preclude the use of the zero point of a particular standard as a true zero point of a particular population and laboratory without experimental verification.*

* Submitted for publication, May 18, 1931.

* This study was carried out under the auspices of the Social Science Research Committee of the University of Chicago.

1. Difference in the zero points of the Krogh and the Mayo standards for men.

Using a portable Benedict apparatus modified by the Sanborn motor blower, I found the zero point (defined as the mean rate) of a group of thirty-four apparently normal male university freshmen to be — 5 per cent, according to the Aub-DuBois standard. With the same type of apparatus, members of the staff of the metabolism laboratory of the University of Chicago Clinics, under the direction of Miss Majorie Smith, made determinations of basal metabolism of 1,126 men and 2,994 women, between January, 1929, and September, 1930;[2] the distributions found are shown diagrammatically in charts 1 and 2. It will be noted that the peak of each distribution is within the normal range, and that each distribution is skewed to the right (in the direction of high rates). This is to be expected, as at least in this locality "hyperthyroidism" is far more common than hypothyroidism. It is

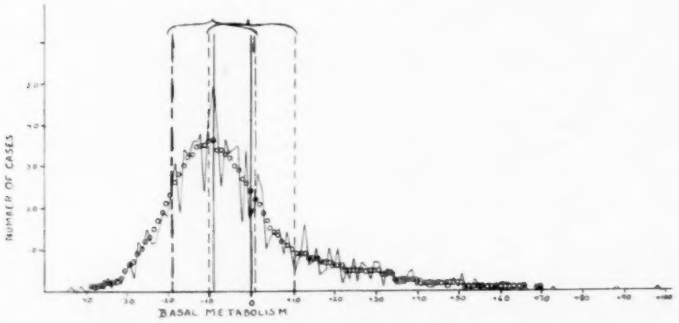

Chart 1.—Distribution of basal metabolism of 1,126 men. These determinations were made in the University of Chicago Clinics.

reasonable to suppose that in that section of the distribution which is within the normal range, there is a preponderance of normal persons, i. e., of those normal with regard to metabolism. If there is such a preponderance of persons with normal metabolism, the greatest number should fall at the zero point. It will be noted that in the case of both men and women the peak of the original curve and the peak of the smoothed curve for women falls at — 9 per cent. The smoothed curve for men is equally high at — 9 per cent and — 10 per cent. The difference between — 5 per cent and — 9 per cent is in part accounted for by the fact that in my data on normal persons, successive determinations on a given day were averaged, while in the data of the clinic the lower reading was selected. This accounts for a discrepancy of from 2 to 2.5 per cent. The remainder is within easy chance

2. The Department of Medicine, University of Chicago Clinics, permitted me to use this material.

deviation, in view of my short series. If the value of the clinic is accepted and successive determinations are averaged, the zero point for this particular locality and technic is —7 per cent. If the lower reading is selected, the zero point is —9 per cent. The importance of the location of the zero point may be realized better if one considers that the conventional 21 per cent range being used as the "normal range" about the zero point, the "normal range" in the data of the clinics may be defined as from — 19 per cent to + 1 per cent instead of from — 10 per cent to + 10 per cent. This would result in a shift of 38 per cent of the women and 37 per cent of the men one way or another across the "limit of the normal range." Incidentally, as a result of such a change, 57 per cent of the women would fall within the normal range in place of 49 per cent and the percentage of men with "normal' rates

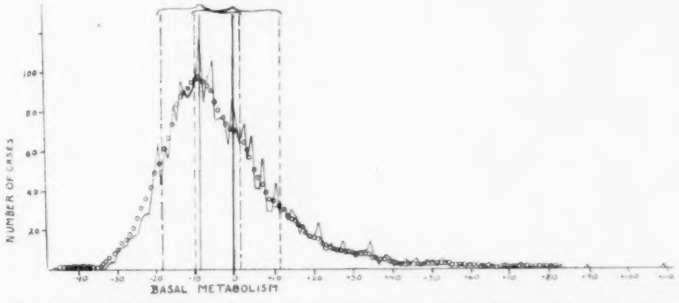

Chart 2.—Distribution of the determinations of basal metabolism of 2,994 women. A portable Benedict apparatus modified by the Sanborn motor blower was used.

would be increased from 45 per cent to 57 per cent. The limits — 10 per cent, + 10 per cent, — 19 per cent and + 1 per cent are indicated on figure 1 and 2.

It may be well here to emphasize that it is highly desirable that each laboratory should individually determine its zero point by the standard it uses. Such a determination should be based on not less than twenty-five normal persons. The determination of the modal point of the distribution of basal rates on a large series of unselected patients may be regarded as a substitute method more open to criticism.

THE NORMAL DISPERSION

It is in a consideration of the "normal dispersion" that the question of random errors of technic must enter. Constant errors will have been taken care of by an adjustment of the zero point. If it were possible to achieve an ideal state, the "normal dispersion" would be reduced

to zero, and the metabolism determinations of all normal persons would fall at the zero point. Under such circumstances, a deviation of 1 per cent from the zero point might be branded as pathologic. This would imply a perfect technic of measurement of gaseous exchange, a perfect "basal state" in every normal person, a perfect normal standard and a perfect application of this standard to each individual. By perfect standard, I mean a standard that would predict exactly the metabolism of any normal individual under the foregoing circumstances. Such a standard lies beyond hope of even ultimate achievement. Experience indicates that under the most favorable conditions one must expect a certain normal dispersion— a dispersion of the metabolism of normal persons, which will certainly remain with the best standard that can ever be devised and the best technic one may ever hope to introduce. Let me here introduce the concept of a true normal dispersion—the dispersion that would remain among "normal" persons if there were a perfect technic, the best possible standard and a constant basal state. Such a true normal dispersion would be less than the normal dispersion that one experimentally observes. The latter is greater because in it one adds the effects of imperfect technic, imperfect standard, imperfect application of the standard (errors in measurement of height and weight) and the fact that a constant "basal condition" is not achieved. These factors all widen the experimental normal dispersion and thereby blunt the technic as a clinical instrument. I proceed, therefore, to a consideration of their influence on the experimental normal dispersion and of how they may be kept at a minimum. I shall choose the standard deviation (σ) as the measure of dispersion.

Then $\sigma_n' = f(\sigma_n, \sigma_t, \sigma_s, \sigma_m, \sigma_b)$, in which σ_n' represents the standard deviation of the experimental normal dispersion; σ_n represents the standard deviation of the true normal dispersion as here defined; σ_t represents the standard error of the technic of measurement of gaseous exchange (or of direct calorimetry); σ_s represents the standard error of the relative prediction value of the standard; σ_m represents the standard error of the application of the standard, and σ_b, the coefficient of variation in the metabolism of normal persons under the condition of basal metabolism determination.

I have indicated that the sharpening of the diagnostic instrument depends on reducing the experimental normal dispersion until it approaches as closely as possible the true normal dispersion. This depends on reducing to as low a level as possible the various errors appearing in the latter part of the expression. I shall consider these separately.

The errors of technic have been the subject of many articles. There is widely a proper respect for them, and effort is directed, with varying

degrees of intensity and success, to their elimination. The importance of this effort is self-evident.

The errors of the standards have been neglected to a greater extent. Table 1, which is condensed from a previous article,[3] contains a tabulation of the coefficient of variation of the error of relative prediction of the basal metabolism of normal persons by the Aub-DuBois standard, the Harris-Benedict standard and the Dreyer standard based on observed weight. It should be noted that these are the errors of relative prediction and not of absolute prediction; each deviation is measured, not from the zero point of the standard, but from the zero point of the group of normal values experimentally determined by this standard. It should further be noted that what actually enters into the determination of normal dispersion is not the coefficient of variability of $\frac{\text{observed calories}}{\text{predicted calories}}$, but the coefficient of variability of $\frac{\text{predicted calories}}{\text{observed calories}}$. The two values may be expected to be practically identical, however, and for the purposes of this comparison this difference is ignored. It will be noted that the Harris-Benedict standard and the Dreyer standard are rather better than the DuBois standard in their accuracy in relative prediction. The weighted mean of the coefficients of variation of the Aub-DuBois standard is 7.505, while the value for the Harris-Benedict standard is 6.605 and that for the Dreyer standard, 6.805. This is a significant improvement.

In the material surveyed by me, the standard of Harris and Benedict, the Dreyer standard based on observed weight and the Boothby and Sandiford standards appear the best by empiric test. The Harris-Benedict standard has the advantage of widely established usage in this country and on the continent of Europe. It necessitates the use of another standard for children. The Dreyer standard and the Boothby-Sandiford standard are applicable to children as young as 5 years of age. The Dreyer standard has an established usage particularly in England. If one uses the tables of Stoner,[4] it is the easiest standard of all to apply.

There is a further procedure by which it is possible to reduce the part played by the error of standard. This consists in the calculation of all borderline or doubtful rates by two or three standards, as this will frequently make a difference of several per cent in the basal rate, even after allowance is made for the differences in the level of the standards. In carrying out this procedure, due allowance should be made for the difference in the level of the standard. Such allowance is conveniently made by the use of tables that I have published.

3. Jenkins, R. L.: Basal Metabolism Standards, J. Nutrition **4**:305, 1931.

4. Stoner, W. H.: Notes on Basal Metabolism, V and VI: Tables of Values of Dreyer's Formulas, Boston M. & S. J. **189**:239, 1923; **191**:1026, 1924.

The error in the application of the standard should be slight, if ordinary care is used. It is not difficult to determine height and weight with a satisfactory degree of accuracy. However, the use of the Dreyer standards based on calculated weight increase these errors materially, as Miss Boyd [5] has pointed out.

The error introduced by the actual variation in the metabolism of a given normal person may be considerable. Wishart [6] found it to be usually in the neighborhood of 5 per cent (coefficient of variation = 5). In my experience with university freshmen, and in the extensive experi-

TABLE 1.—*Probability of Deviation of Normal Persons*

Deviation From Zero Point, per Cent	Probability
5	1 chance in 4
10	1 chance in 13
15	1 chance in 63
17	1 chance in 132
20	1 chance in 455

TABLE 2.—*Prediction Accuracy of Various Standards on Adults*

Investigator	Number of Subjects	Sex	Coefficient of Variation*		
			Aub-Dubois Standard	Harris-Benedict Standard	Dreyer-Standard (Observed Weight)
Harris and Benedict	134	M	8.59	**6.10**	6.58
Harris and Benedict	102	F	7.82	7.85	**7.68**
Boothby and Sandiford	41	M	6.19	**5.95**	5.96
Boothby and Sandiford	61	F	**5.59**	5.85	6.17
Earle	87†	M	7.13	**6.59**	6.85
Hobson	46	M	....	7.19	**6.10**
Author	34	M	8.27	7.04	7.11
Mean (excluding Hobson)			7.265	6.563	6.725
Mean (excluding Hobson) weighted for number of cases			7.505	6.605	6.805

* Coefficient of variation of $\frac{\text{predicted calories}}{\text{observed calories}}$

† These subjects were Chinese.

ence of Dr. Kunde of this university with dogs, there is considerable difference between persons in the extent to which their metabolism tends to vary. This source of error is reduced to a minimum by observing carefully the standard procedures for inducing a basal condition and by making repeated tests in doubtful cases, training the subjects to relax.

Any definition of "normal range of basal metabolism" is necessarily arbitrary. There is, of course, a gradual diminution in the likelihood

5. Boyd, Edith: The Experimental Error Inherent in Measuring the Growing Human Body, Am. J. Phys. Anthropol. **13**:389, 1929.

6. Wishart, George: The Variability of Basal Metabolism, Quart. J. Med. **20**: 193, 1927.

that a given person's metabolism is normal, as our measurement shows it to deviate from the zero point. If 7 is accepted as a typical coefficient of variation of the basal metabolic rates of normal persons tested with careful technic, the probability is that a normal person will deviate any given distance in a given direction from the mean, as tabulated in table 1. It is obvious that a normal range of 10 per cent is dangerously small, as two normal persons in thirteen may be expected to fall outside the normal range, one at either end.

Of course, the same series of normal persons used to determine the "zero point" in any given laboratory may also be used to determine the normal dispersion for that laboratory by a calculation of the coefficient of variation. Chance factors in the selection of "normals" will enter into the coefficient of variation unless a fair series is used.

SUMMARY AND CONCLUSIONS

1. Every laboratory should determine the "zero point" of its own normal population and its own technic on the standard it uses. This may be carried out by determinations on a minimum of twenty-five normal persons or by taking the modal point of a very large series of unselected cases.

2. The experimental normal range is a function of the true normal range and the errors of measurement. With good technic, it is possible to reduce the normal range to a minimum and so sharpen basal metabolism determination as a diagnostic instrument.

3. The use of the Harris-Benedict standard or the Dreyer standard based on observed weight reduces the normal range as compared with the Aub-DuBois standard.

4. The error introduced by the standard may be further reduced by comparing two or three standards in all doubtful cases.

5. A delimitation of the normal range to 21 per cent is probably overly low, even with a good technic. This might be supplemented by regarding all cases deviating from 10 to 17 per cent from the zero point as "doubtful."

BASAL METABOLISM

II. THE BASAL PULSE COMPLEX *

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The importance of the elevation of pulse rate and pulse pressure in the diagnosis of disturbances of the thyroid has long been recognized. Despite the importance of these symptoms and the fact that they are easily available to quantitative treatment, their clinical use is largely by rule of thumb. Since their value is so generally recognized by rule of thumb methods, it seems not unreasonable to suppose that it might be considerably increased by the application of more precise methods of study and use.

In 1924, Read published a formula for the prediction of basal metabolism from basal pulse rate and basal pulse pressure.[1] The formula is 0.75 (pulse rate + 0.74 pulse pressure) — 72 = basal rate. Read stated that by this formula it was possible to predict the basal metabolic rate within 10 per cent in a little more than half of the cases.

Hunt compared basal rate and Read's formula in 54 cases. Four basal determinations were rejected as unreliable. Of the remaining 50 cases, in 27 (54 per cent) the basal rate and the value from Read's formula agreed within 10 per cent. Hunt is quoted by Langmead [2] as drawing the following conclusions:

1. Read's formula will very seldom give appreciably too high an estimate of the basal metabolic rate, but often gives slightly lower figures.

2. A very marked discrepancy suggests an error in technique.

3. The basal metabolic rate in very bad cases is probably fairly considerably higher than Read's formula suggests.

4. Iodine treatment appears to improve the circulatory system as shown by Read's formula more definitely and more permanently than it improves the basal metabolic rate, which does not appear to be reduced for long by the comparatively small doses given (up to 20 minims of Lugol's solution daily). With this exception Read's formula has shown improvement in treatment exactly parallel with that shown by the basal metabolic rate.

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* Submitted for publication, May 18, 1931.

* This study was carried out under the auspices of the Social Science Research Committee of the University of Chicago.

1. Read, J. Marion: Basal Pulse Rate and Pulse Pressure Changes Accompanying Variations in Basal Metabolic Rate, Arch. Int. Med. **34**:553 (Oct.) 1924.

2. Langmead, F. S.: The Etiology, Prognosis and Treatment of Graves' Disease, Brit. M. J. **1**:715, 1929.

5. Read's formula should be applied under basal conditions but does not seem to vary so much as the basal metabolic rate from food or other external factors. In some cases it is quite impossible to gauge this latter accurately. Within limits it would seem that the figure obtained by this formula is an accurate guide to progress, and differs widely from the basal metabolic rate figure only in the severest cases. It has a particular field of usefulness when for some reason estimation of the basal metabolic rate is not practicable.

In view of the fact that it is a quite widespread practice to take the pulse under basal conditions at the time the basal metabolism is determined, and that it is very simple to add a determination of blood pressure, it seems strange that this formula has not come into rather general use in connection with the actual determination of basal metabolism. Its value by such an arrangement would not lie in predicting the basal rate, since this can be experimentally measured with considerably more accuracy, but rather in affording a "pulse complex" figure which would be directly comparable with the basal rate and afford a confirmatory diagnostic measure.

SOURCE OF MATERIAL

The material used for this study consists of 4,120 routine basal metabolism determinations. These determinations comprise all of the determinations made on subjects 16 or more years of age in the metabolism laboratory of the University of Chicago Clinics from January, 1929, to September, 1930. All determinations were made by or under the direction of Miss Marjorie Smith who was in charge of the laboratory. This material has been used by permission of the department of medicine of the University of Chicago.

The procedure was as follows: The patient appeared (from home or from the hospital) in the metabolism laboratory without breakfast and without a bath. After being weighed (in cotton gown) and measured, the patient rested in bed for one-half hour. Toward the end of this period of rest the temperature was taken and the pulse was counted for one minute. Two determinations of oxygen consumption were performed with the Benedict closed circuit apparatus modified with the Sanborn motor blower. At the end of the second determination, without disturbing the patient, the blood pressure was measured two or three times with a mercury sphygmomanometer and an average value was recorded.

PROCEDURE OF STATISTICAL ANALYSIS

From the outset, men and women were treated separately. The original plan included the treatment of seven variables. These variables were basal metabolic rate, pulse rate, respiration rate, body temperature, systolic blood pressure, diastolic blood pressure and age. It was found by experimental tabulations that pulse pressure bore a higher correlation with basal metabolism than did either systolic blood pressure or diastolic

blood pressure. Pulse pressure was therefore substituted for these two measures. Preliminary tabulations also revealed the absence of any relation between age and basal metabolic rate or age and pulse rate, and the relations between age and respiration rate, age and body temperature, and age and pulse pressure were of such low degree that it was decided to ignore them and eliminate age as a variable. The number of variables was thus reduced to five.

TABLE 1.—*Intercorrelation of Basal Metabolic Rate, Pulse Rate, Pulse Pressure, Respiration Rate and Body Temperature*

Correlation of	846 Men	2,408 Women
Basal metabolic rate and pulse rate	$r_{12} = 0.525 \pm 0.017$	$r_{12} = 0.504 \pm 0.010$
Basal metabolic rate and pulse pressure	$r_{13} = 0.507 \pm 0.018$	$r_{13} = 0.448 \pm 0.011$
Basal metabolic rate and respiration rate	$r_{14} = 0.281 \pm 0.021$	$r_{14} = 0.308 \pm 0.012$
Basal metabolic rate and body temperature	$r_{15} = 0.233 \pm 0.022$	$r_{15} = 0.178 \pm 0.013$
Pulse rate and pulse pressure	$r_{23} = 0.394 \pm 0.020$	$r_{23} = 0.268 \pm 0.013$
Pulse rate and respiration rate	$r_{24} = 0.254 \pm 0.022$	$r_{24} = 0.219 \pm 0.013$
Pulse rate and body temperature	$r_{25} = 0.262 \pm 0.022$	$r_{25} = 0.289 \pm 0.012$
Pulse pressure and respiration rate	$r_{34} = 0.206 \pm 0.022$	$r_{34} = 0.184 \pm 0.013$
Pulse pressure and body temperature	$r_{35} = 0.154 \pm 0.023$	$r_{35} = 0.145 \pm 0.013$
Respiration rate and body temperature	$r_{45} = 0.048 \pm 0.023$	$r_{45} = 0.073 \pm 0.013$

TABLE 2.—*Mean Value of Basal Metabolic Rate, Pulse Rate, Pulse Pressure, Respiration Rate and Body Temperature*

Variable	Mean Value of Each Variable	
	Men	Women
1. Basal metabolic rate	−3.2% ± 0.63	−2.8% ± 0.34
2. Pulse rate	73.3 ± 0.45	81.3 ± 0.28
3. Pulse pressure	43.9 ± 0.51	44.3 ± 0.31
4. Respiration rate	14.03 ± 0.14	14.68 ± 0.08
5. Body temperature	97.7° ± 0.02	98.1° ± 0.01

TABLE 3.—*Standard Deviation of Basal Metabolic Rate, Pulse Rate, Pulse Pressure, Respiration Rate and Body Rate*

Variable	Standard Deviation of Each Variable	
	Men	Women
1. Basal metabolic rate	18.3% ± 0.44	16.7% ± 0.24
2. Pulse rate	13.2 ± 0.32	13.9 ± 0.20
3. Pulse pressure	14.9 ± 0.36	15.3 ± 0.22
4. Respiration rate	4.16 ± 0.10	4.12 ± 0.06
5. Body temperature (Fahrenheit)	0.66° ± 0.02	0.61° ± 0.01

The first step in the analysis was to prepare correlation sheets and calculate correlation coefficients for each of the ten interrelations of these measures. The results of this treatment are contained in tables 1, 2 and 3. Correlation coefficients of basal metabolism with pulse rate and pulse pressure are not so large as those obtained by Read, but are practically identical with the findings of Minot and Means.

Read obtained from 600 basal tests on both men and women a correlation between basal metabolic rate and pulse rate of 0.745

± 0.013 and between basal metabolic rate and pulse pressure of 0.625 ± 0.015. Minot and Means [3] found a correlation of 0.525 ± 0.036 between basal metabolism and pulse rate in the case of 180 observations on 126 patients with hyperthyroidism and a coefficient of 0.544 ± 0.044 in the case of 110 observations on 71 patients with leukemia. Sturgis and Tompkins [4] and James Smith [5] have published scatter diagrams of the relation between pulse rate and basal metabolism. Davies, Meakins and Sands [6] have published a scatter diagram of basal metabolic rate and minute volume of cardiac output. These tables all show a pronounced relationship. The authors have not calculated correlation coefficients.

The fact that a lower correlation coefficient was obtained with the data here presented than that of Read is to be ascribed largely to the fact that the material of Read contained proportionately fewer cases within the normal range and more outside of it. Such a widening of the range would, of course, result in a higher correlation coefficient.

The next step in the analysis of the data here presented consisted in the application of multiple correlation technic to determine the best weighting of a regression equation for basal metabolism. Table 4 contains the multiple correlation coefficients of basal metabolism with pulse rate and pulse pressure and of basal metabolism with pulse rate, pulse pressure and respiration rate, together with the probable error of prediction for each. It becomes evident that the increase in prediction accuracy to be gained by the inclusion of body temperature as a fourth factor will be insignificant. Indeed, the gain in prediction accuracy from the inclusion of respiration rate in the prediction is inadequate to justify the added complexity its inclusion brings.

The regression equation for the prediction of the basal metabolism of men from their basal pulse rate and basal pulse pressure, as derived from this material, is 0.534 pulse rate + 0.436 pulse pressure —62.55. That for women is 0.497 pulse rate + 0.368 pulse pressure —59.51. These two formulas form an interesting comparison to the equation of Read, which is 0.75 pulse rate + 0.57 pulse pressure —72. All the formulas give about the same proportionate weight to pulse rate and pulse pressure.

3. Minot, G. R., and Means, J. H.: The Metabolism-Pulse Ratio in Exophthalamic Goiter and in Leukemia, Arch. Int. Med. **33**:576 (May) 1924.

4. Sturgis, C. C., and Tompkins, E. H.: A Study of the Correlation of the Basal Metabolism and Pulse Rate in Patients with Hyperthyroidism, Arch. Int. Med. **24**:467 (Oct.) 1920.

5. Smith, J. H.: Basal Metabolism: I. Correlation of Basal Metabolic Rate and Basal Pulse Rate, Arch. Int. Med. **41**:663 (May) 1928.

6. Davies, H. W.; Meakins, J., and Sands, J.: The Influence of Circulatory Disturbances on the Gaseous Exchange of the Blood: V. The Blood Gases and Circulation Rate in Hyperthyroidism, Heart **11**:299, 1924.

Certain sources of error should be considered in evaluating the foregoing procedures. In the first place, the lower of two rates has uniformly been selected as the true basal rate. As there has been no similar selection of the lower of two pulse complexes, this does not seem a justified procedure. The mean difference between the lower and the higher of two rates taken in succession during the same metabolism period is 5.29 per cent in the case of the men and 4.17 per cent in the case of the women. If one-half this correction is added to the foregoing prediction formulas to give the best prediction of midbasal rate, the formulas become:

$$0.534 \text{ pulse rate} + 0.436 \text{ pulse pressure} - 59.94$$

and

$$0.497 \text{ pulse rate} + 0.368 \text{ pulse pressure} - 57.42$$

Random errors in the determination (or variation within the given period) of any variable entering into the formula would reduce the correlation. The degree of random error in the determination of basal metabolism becomes evident from an analysis of the cases of 291 men and 765 women on whom both basal rates were tabulated. The reliability of the method is 0.922 ± 0.006 in the case of the men and 0.940 ± 0.003 in the case of the women. If Spearman's formula for correction of the attenuation of basal metabolism is applied, the multiple coefficient of correlation of basal metabolism with pulse rate and pulse pressure is raised from 0.598 to 0.613 in the case of the men, while that of the women rises from 0.600 to 0.619. It is evident that error in the determination of basal metabolism exerts no significant influence over the relation as here described. It is not possible from the available data to determine the degree or influence of the error in the determination of pulse rate or pulse pressure, nor would it be theoretically permissible to correct for the attenuation of these measures if this could be done, since the error of these measurements must inevitably enter into any use that is made of them. The error in the determination of pulse rate may be expected to be low. That in the determination of pulse pressure is probably considerable.

Inspection of table 1 may already have called to the attention of the reader the fact that most of the variables correlate with basal metabolism more highly than with any other variable. This introduces the question of whether the intercorrelations of pulse rate, pulse pressure, respiration rate and body temperature with each other are due simply to the fact that each is correlated with basal metabolism. Is the association of rapid respiration and rapid pulse simply a reflection of the fact that both are commonly associated with an elevated basal metabolism, or does the pulse per se exert some influence over the respiration or vice versa? This question may be answered by observing the partial

correlation coefficients of pulse rate, pulse pressure, respiration rate, and body temperature with basal metabolism constant. These coefficients are tabulated in table 5.

A survey of table 5 will reveal that these partial coefficients of correlation are all low, but with one exception are all positive. The conclusion indicated seems to be that most, but not all, of the intercorrelation of pulse rate, pulse pressure, respiration rate and body temperature is due to the correlation of each of these measures with basal metabolism.

It may further be stated that this material indicates that rise of 1 degree Fahrenheit is equal to a rise in basal rate of 7 per cent in the case of men or 5 per cent in the case of the women. One degree centi-

TABLE 4.—*Multiple Correlation Coefficients for Prediction of Basal Metabolic Rate*

	Multiple Correlation Coefficient			Probable Error of Prediction of Basal Rate
Men				
Basal metabolic rate with pulse rate and pulse pressure	$r_{1.23}$	=	0.508	9.90%
Basal metabolic rate with pulse rate, pulse pressure and respiration rate	$r_{1.234}$	=	0.629	9.59%
Women				
Basal metabolic rate with pulse rate and pulse pressure	$r_{1.23}$	=	0.600	9.01%
Basal metabolic rate with pulse rate, pulse pressure and respiration rate	$r_{1.234}$	=	0.621	8.83%

TABLE 5.—*Partial Intercorrelation Coefficients with Basal Metabolic Rate Constant*

Partial Correlation of	Men			Women		
Pulse rate and pulse pressure	$r_{23.1}$	=	0.175	$r_{23.1}$	=	0.054
Pulse rate and respiration rate	$r_{24.1}$	=	0.130	$r_{24.1}$	=	0.078
Pulse rate and body temperature	$r_{25.1}$	=	0.166	$r_{25.1}$	=	0.269
Pulse pressure and respiration rate	$r_{34.1}$	=	0.075	$r_{34.1}$	=	0.085
Pulse pressure and body temperature	$r_{35.1}$	=	0.041	$r_{35.1}$	=	0.074
Respiration rate and body temperature	$r_{45.1}$	=	−0.019	$r_{45.1}$	=	0.019

grade is the equivalent of 12 per cent for the women and of 9 per cent for the men. These figures agree fairly well with those of DuBois [7] (7.2 per cent for each degree Fahrenheit, 13 per cent for each degree centigrade).

THE VALUE OF BASAL PULSE COMPLEX

For an experimental trial of the three formulas, a retabulation was made of the basal metabolism determinations on 55 men and 120 women. These determinations were selected to secure a wide spread of basal rates and included only cases in which two successive basal rates differed by less than 5 per cent. The correlation of the lower basal rate with each of the formulas and with pulse rate × pulse pressure is given in

7. DuBois, E. T.: Basal Metabolism in Health and Disease, ed. 2, Philadelphia, Lea & Febiger, 1927, p. 389.

table 8. A scatter diagram of the agreement of basal pulse complex with basal rate is given in chart 1. It will be noted that 15 of 18 women having a basal pulse complex of + 15 per cent or more have a basal rate of + 15 per cent or more, and two of the remaining 3 have a basal rate of + 10 per cent + 14 per cent. Four of 5 women having a pulse complex of —15 per cent or less also have a basal rate of —15 per cent or less. This indicates a high degree of validity for the basal pulse complex in the diagnosis of disorders of metabolism.

Despite the circular reasoning involved in the use of a measure developed from its agreement with basal metabolism as a check on

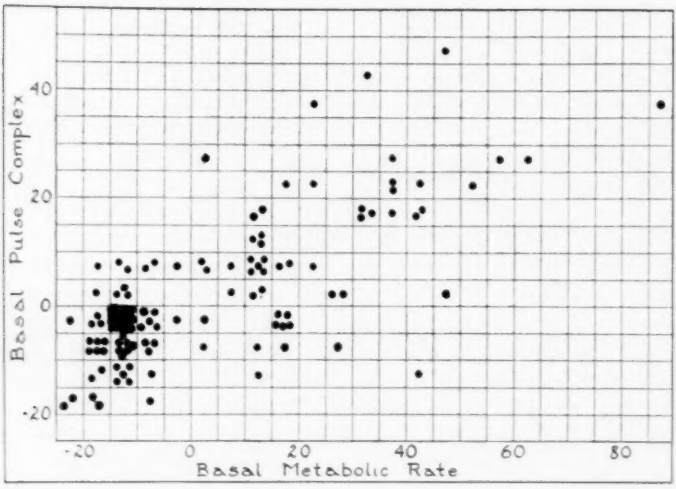

Chart. 1.—Scatter diagram showing agreement of basal pulse complex with basal rate.

basal metabolism determinations, I am of the opinion that there is a definite place in clinical diagnosis for the use of such a measure as the prediction formula of Read or the basal pulse complex devised here. The importance of pulse rate and pulse pressure in the diagnosis of thyrotoxicosis and of myxedema is generally recognized. The value of these should be decidedly increased if rule of thumb methods are abandoned in favor of determination of basal pulse rate and basal pulse pressure and satisfactory formulas are applied.

It should be recognized that such a formula cannot be regarded as a substitute for basal metabolism determination, unless under conditions in which the latter cannot be secured. It should be recognized that basal pulse complex is not to be given equal clinical weight with basal metabolism. Nevertheless, as a confirmatory measure, particularly in the

diagnosis of doubtful cases, and in following the course of disease, it recommends itself to serious consideration. Chart 2 illustrates the course of basal metabolism and basal pulse complex in a patient with thyroid disease. This patient was treated with compound solution of

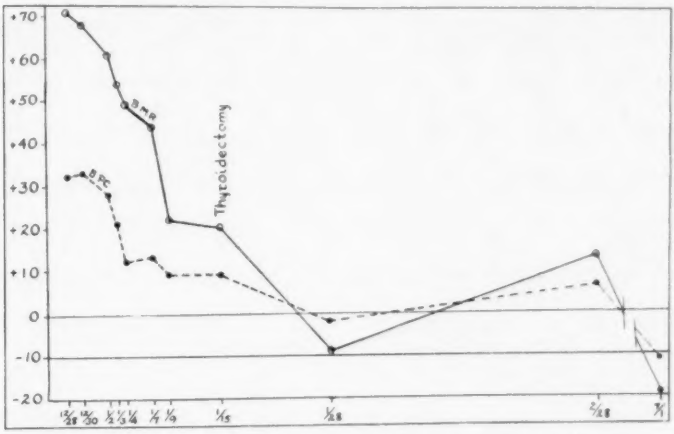

Chart 2.—Course of basal metabolism and basal pulse complex in a man with diffuse hyperplastic goiter with severe hyperthyroidism.

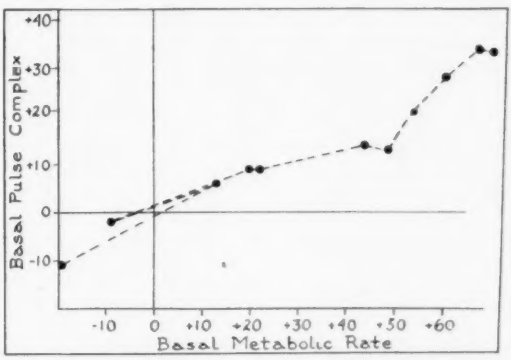

Chart 3.—Basal pulse complex plotted against basal metabolic rate in the case of a man with diffuse hyperplastic goiter with severe hyperthyroidism.

iodine and subjected to thyroidectomy with good results. It will be observed that while basal pulse complex does not deviate as far in either direction in this extreme case as basal metabolic rate, yet the parallelism of the two is almost perfect. This is perhaps more clearly demonstrated in chart 3. In chart 3 the line of dots approaches a straight line, indi-

TABLE 6.—*Basal Pulse Complex in Men*

Pulse Pressure	Pulse Rate																						
	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
15	−32	−29	−27	−24	−21	−19	−16	−13	−11	− 8	− 5	− 3	0	+ 3	+ 5	+ 8	+11	+13	+16	+19	+21	+24	+27
20	−30	−27	−25	−22	−19	−17	−14	−11	− 9	− 6	− 3	0	+ 2	+ 5	+ 8	+10	+13	+16	+18	+21	+24	+26	+29
25	−28	−25	−22	−20	−17	−14	−12	− 9	− 6	− 4	− 1	+ 2	+ 4	+ 7	+10	+12	+15	+18	+20	+23	+26	+28	+31
30	−26	−23	−20	−17	−15	−12	− 9	− 7	− 4	− 2	+ 1	+ 4	+ 7	+ 9	+12	+15	+17	+20	+23	+25	+28	+31	+33
35	−23	−21	−18	−15	−13	−10	− 7	− 5	− 2	+ 1	+ 3	+ 6	+ 9	+11	+14	+17	+19	+22	+25	+27	+30	+33	+35
40	−21	−18	−16	−13	−10	− 8	− 5	− 2	0	+ 3	+ 6	+ 8	+11	+14	+16	+19	+22	+24	+27	+30	+32	+35	+38
45	−19	−16	−14	−11	− 8	− 6	− 3	0	+ 2	+ 5	+ 8	+10	+13	+16	+18	+21	+24	+26	+29	+32	+34	+37	+40
50	−17	−14	−11	− 9	− 6	− 3	− 1	+ 2	+ 5	+ 7	+10	+13	+15	+18	+21	+23	+26	+29	+31	+34	+37	+39	+42
55	−15	−12	− 9	− 7	− 4	− 1	+ 1	+ 4	+ 7	+ 9	+12	+15	+17	+20	+23	+25	+28	+31	+33	+36	+39	+41	+44
60	−12	−10	− 7	− 4	− 2	+ 1	+ 4	+ 6	+ 9	+12	+14	+17	+20	+22	+25	+28	+30	+33	+36	+38	+41	+44	+46
65	−10	− 7	− 5	− 2	0	+ 3	+ 6	+ 8	+11	+14	+16	+19	+22	+24	+27	+30	+33	+35	+38	+40	+43	+46	+49
70	− 8	− 5	− 3	0	+ 3	+ 5	+ 8	+11	+13	+16	+19	+21	+24	+27	+29	+32	+35	+37	+40	+43	+45	+48	+51
75	− 6	− 3	0	+ 2	+ 5	+ 7	+10	+13	+15	+18	+21	+23	+26	+29	+32	+34	+37	+40	+42	+45	+48	+50	+53
80	− 4	− 1	+ 2	+ 4	+ 7	+10	+12	+15	+18	+20	+23	+26	+28	+31	+34	+36	+39	+42	+44	+47	+50	+52	+55
85	− 1	+ 1	+ 4	+ 7	+ 9	+12	+15	+17	+20	+23	+25	+28	+31	+33	+36	+39	+41	+44	+47	+49	+52	+55	+57
90	+ 1	+ 4	+ 6	+ 9	+11	+14	+17	+19	+22	+25	+27	+30	+33	+35	+38	+41	+43	+46	+49	+51	+54	+57	+59
95	+ 3	+ 6	+ 8	+11	+14	+16	+19	+22	+24	+27	+30	+32	+35	+38	+40	+43	+46	+48	+51	+54	+56	+59	+62
100	+ 5	+ 8	+10	+13	+16	+18	+21	+24	+26	+29	+32	+34	+37	+40	+42	+45	+48	+50	+53	+56	+58	+61	+64
105	+ 7	+10	+13	+15	+18	+21	+23	+26	+29	+31	+34	+37	+39	+42	+45	+47	+50	+53	+55	+58	+61	+63	+66
110	+ 9	+12	+15	+18	+20	+23	+25	+28	+31	+33	+36	+39	+41	+44	+47	+49	+52	+55	+57	+60	+63	+65	+68
115	+12	+15	+17	+20	+22	+25	+28	+30	+33	+36	+38	+41	+44	+46	+49	+51	+54	+57	+59	+62	+65	+68	+70
120	+14	+17	+19	+22	+24	+27	+30	+32	+35	+38	+40	+43	+46	+48	+51	+53	+56	+59	+61	+64	+67	+70	+72

TABLE 7.—*Basal Pulse Complex in Women*

Pulse Pressure	Pulse Rate																						
	40	45	50	55	60	65	70	75	80	85	90	95	100	105	110	115	120	125	130	135	140	145	150
15	−32	−30	−27	−25	−22	−20	−17	−15	−12	−10	− 7	− 5	− 2	0	+ 3	+ 5	+ 8	+10	+13	+15	+18	+20	+23
20	−30	−28	−25	−23	−20	−18	−15	−13	−10	− 8	− 5	− 3	0	+ 2	+ 5	+ 7	+ 9	+12	+14	+17	+19	+22	+24
25	−28	−26	−23	−21	−18	−16	−13	−11	− 8	− 6	− 3	− 1	+ 1	+ 4	+ 6	+ 9	+11	+14	+16	+19	+21	+24	+26
30	−27	−24	−22	−19	−17	−14	−12	− 9	− 7	− 4	− 2	+ 1	+ 3	+ 6	+ 8	+11	+13	+16	+18	+21	+23	+26	+28
35	−25	−22	−20	−17	−15	−12	−10	− 7	− 5	− 2	0	+ 3	+ 5	+ 8	+10	+13	+15	+18	+20	+23	+25	+28	+30
40	−23	−20	−18	−15	−13	−10	− 8	− 5	− 3	0	+ 2	+ 4	+ 7	+ 9	+12	+14	+17	+19	+22	+24	+27	+29	+32
45	−21	−19	−16	−14	−11	− 9	− 6	− 4	− 1	+ 1	+ 4	+ 6	+ 9	+11	+14	+16	+19	+21	+24	+26	+29	+31	+34
50	−19	−17	−14	−12	− 9	− 7	− 4	− 2	+ 1	+ 3	+ 6	+ 8	+11	+13	+16	+18	+21	+23	+26	+28	+30	+33	+36
55	−17	−15	−12	−10	− 7	− 5	− 2	0	+ 3	+ 5	+ 8	+10	+13	+15	+17	+20	+22	+25	+27	+30	+32	+35	+37
60	−15	−13	−10	− 8	− 6	− 3	− 1	+ 2	+ 4	+ 7	+ 9	+12	+14	+17	+19	+22	+24	+27	+29	+32	+34	+37	+39
65	−14	−11	− 9	− 6	− 4	− 1	+ 1	+ 4	+ 6	+ 9	+11	+14	+16	+19	+21	+24	+26	+29	+31	+34	+36	+39	+41
70	−12	− 9	− 7	− 4	− 2	+ 1	+ 3	+ 6	+ 8	+11	+13	+15	+18	+21	+23	+26	+28	+30	+33	+35	+38	+40	+43
75	−10	− 7	− 5	− 2	0	+ 2	+ 5	+ 7	+10	+12	+15	+17	+20	+22	+25	+27	+30	+32	+35	+37	+40	+42	+45
80	− 8	− 6	− 3	− 1	+ 2	+ 4	+ 7	+ 9	+12	+14	+17	+19	+22	+24	+27	+29	+32	+34	+37	+39	+41	+44	+47
85	− 6	− 4	− 1	+ 1	+ 4	+ 6	+ 9	+11	+14	+16	+19	+21	+24	+26	+29	+31	+33	+36	+38	+41	+43	+46	+48
90	− 5	− 2	0	+ 3	+ 5	+ 8	+11	+13	+15	+18	+20	+23	+25	+28	+30	+33	+35	+38	+40	+43	+45	+48	+50
95	− 3	0	+ 2	+ 5	+ 7	+10	+12	+15	+17	+20	+22	+25	+27	+30	+32	+35	+37	+40	+42	+45	+47	+50	+52
100	− 1	+ 2	+ 4	+ 7	+ 9	+12	+14	+17	+19	+22	+24	+27	+29	+32	+34	+37	+39	+42	+44	+46	+49	+51	+54
105	+ 1	+ 3	+ 6	+ 8	+11	+13	+16	+18	+21	+23	+26	+28	+31	+33	+36	+38	+41	+43	+46	+48	+51	+53	+56
110	+ 3	+ 5	+ 8	+10	+13	+15	+18	+20	+23	+25	+28	+30	+33	+35	+38	+40	+43	+45	+48	+50	+52	+55	+58
115	+ 5	+ 7	+10	+12	+15	+17	+20	+22	+25	+27	+30	+32	+35	+37	+40	+42	+44	+47	+49	+52	+54	+57	+59
120	+ 7	+ 9	+12	+14	+16	+19	+21	+24	+27	+29	+31	+34	+36	+39	+41	+44	+46	+49	+51	+54	+56	+59	+61

cating a very close correspondence between basal rate and basal pulse complex. Chart 3 suggests that basal pulse complex gains greater validity as an individualized measure for following a particular patient.

Read's formula gives a prediction that is typically about 10 per cent higher than the basal pulse complex of normal subjects. This difference is perhaps associated with the low level of metabolism obtained in the metabolism laboratories at the University of Chicago. Read's formula also tends to emphasize deviation more than the basal pulse complex. All that I am able to state regarding the relative merits of the two are that the basal pulse complex is based on a much larger series and fits that series better than Read's formula. It is possible that it will be somewhat low or somewhat high for other laboratories.

Tables 6 and 7 are conveniently arranged for the determination of basal pulse complex. After locating the pulse rate column and the pulse pressure row, one directly reads off the basal pulse complex at the junc-

TABLE 8.—*Correlation of Various Prediction Formulas with Basal Rate (One Hundred and Twenty Women)*

Basal pulse complex with basal rate	$r = 0.73 \pm 0.029$
Read's formula with basal rate	$r = 0.64 \pm 0.036$
Pulse rate × pulse pressure with basal rate	$r = 0.68 \pm 0.033$

	Mean	Standard Deviation
Basal metabolic rate	+ 4.38%	22.1%
Basal pulse complex	+ 3.04%	13.1%
Read's formula	+17.38%	20.4%
Pulse rate × pulse pressure	−41.0	22.4

tion of the two. With these tables, 62 basal pulse complex determinations were made on 14 apparently normal university freshmen. The mean value obtained was —13 per cent and the standard deviation 6.77 per cent (probable error = ±4.56 per cent). This mean seems very low, but one must remember that the mean basal metabolic rate simultaneously taken for this series was —5.5 per cent and the standard deviation was 9.2 per cent (probable error = ±6.2 per cent). The difference in the two means is 7.5 per cent. This may be in part accounted for by the fact that the series is very short, and the size of the standard deviation of basal metabolic rate suggests that the sampling is erratic. A second possible contributing factor is the fact that in these cases the pulse was taken during the actual test, while in the clinic series it was taken toward the end of the half hour rest period. Probably the most important factor, however, is that in the clinic series the portion of persons with a slight tachycardia of nervous origin is almost certainly higher than in normal freshmen, since it is these cases that excite the suspicion of hyperthyroidism. For differential diagnosis of such cases a formula based on clinic material in which they are well represented should be of greater value than one based on a truly normal population.

It should be noted in closing that if basal pulse complex is compared with any other basal metabolism standard than the Aub-DuBois, allowance for difference in the level of the metabolism standards should be made in a manner previously outlined.[8]

CONCLUSIONS

Formulas and tables are here presented for the calculation of a basal pulse complex which is comparable with the basal metabolism of adults.

This measure should be of value as a procedure supplementary and confirmatory to basal metabolism determination in the diagnosis of metabolic disease.

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8. Jenkins, R. L.: Basal Metabolism: I. The Error of Basal Metabolism Determination and the Normal Range of Basal Metabolism, Arch. Int. Med., this issue, p. 181.

THE RANGE OF EFFECTIVE IODINE DOSAGE IN EXOPHTHALMIC GOITER

IV. THE EFFECT ON BASAL METABOLISM OF THE DAILY ADMINISTRATION OF ABOUT 0.75 MG. OF IODINE *

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We have previously shown that in Boston the daily administration of about 6 mg. of iodine in the form of the compound solution produces a maximum reduction in basal metabolism in most hospital patients with exophthalmic goiter,[1] and that the daily administration of about 3 mg. produces on the average only half as much reduction [2] and the daily administration of about 1.5 mg. on the average only one-third as much reduction.[3] As a continuation of our study of the range of effective iodine dosage in exophthalmic goiter we have now investigated the effect of the daily administration of about 0.75 mg. of iodine in twelve unselected hospital patients with the disease.

METHOD AND RESULTS

Method.—The same routine was followed as with the hospital patients in the first paper of this series,[1] except that 1 drop of a 12.5 per

* Submitted for publication, April 21, 1931.

* From the Metabolism Laboratory and Thyroid Clinic of the Massachusetts General Hospital, Boston. This paper was written after the first two authors had started work at the Rush Medical College and the Presbyterian Hospital, Chicago.

1. Thompson, W. O.; Brailey, A. G.; Thompson, P. K., and Thorp, E. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: I. The Effect on Basal Metabolism of Rest and of the Daily Administration of One Drop of Compound Solution of Iodine, Arch. Int. Med. **45**:261 (Feb.) 1930.

2. Thompson, W. O.; Thorp, E. G.; Thompson, P. K., and Cohen, A. C.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: II. The Effect on Basal Metabolism of the Daily Administration of One-Half Drop of Compound Solution of Iodine, Arch. Int. Med. **45**:420 (March) 1930.

3. Thompson, W. O.; Cohen, A. C.; Thompson, P. K.; Thorp, E. G., and Brailey, A. G.: The Range of Effective Iodine Dosage in Exophthalmic Goiter: III. The Effect on Basal Metabolism of the Daily Administration of One-Quarter Drop of Compound Solution of Iodine and Slightly Smaller Doses, with a Summary of Results to Date, Arch. Int. Med. **45**:430 (March) 1930.

TABLE 1.—*Summary of the Consecutive Effects of Rest, the Daily Administration*
in Hospital Patients

Patient	Laboratory Number	Age	Height, Cm.	Admission: Basal Metabolic Rate, per Cent of Normal	Admission: Pulse Rate	Admission: Weight, Kg.	Rest: Average Level of Basal Metabolic Rate, per Cent of Normal	Rest: Pulse Rate	Rest: Weight, Kg.	Rest: Change in Basal Metabolic Rate, Points	Rest: Number of Days Before Level Was Reached	Rest: Length of Time Effect Was Observed, Days
Mrs. G. H.	1340	42	156	+69	107	52.9	+48	99	51.6	—21	1	3
Mr. G. C.	6711	57	173	+38	115	58.9	+40	93	57.7	+ 2	0	4
Mrs. L. P.	6723	23	160	+81	118	48.4	+64	100	45.5	—17	1	6
Mrs. M. M.	6727	52	154	+56	102	43.7	+33	88	43.9	—23	1-2	7
Mr. P. G.	6746	28	178	+47	120	49.3	+33	103	48.5	—14	1-3	6
Mr. C. F.	6752	49	174	+40	104	59.4	+26	81	58.2	—14	4	6
Miss L. L.	6771	18	155	+57	103	34.5	+38	94	34.6	—19	1	6
Mr. W. T.	6799	41	162	+53	112	43.1	+39	87	43.3	—14	1-2	6
Mrs. E. P.	6885	22	162	+52	116	48.7	+36	105	49.0	—16	2	3
Mr. A. C.	6894	26	171	+41	87	55.8	+31	73	54.0	—10	4	7
Mrs. M. G.	6956	38	160	+65	128	52.9	+43	93	53.1	—22	1-2	4
Mr. E. B.	6994	32	166	+40	76	49.6	+33	72	50.5	— 7	1	4
Average all cases (12)				+53			+39			—15		5
Average all cases in which the basal metabolic rate dropped 10 points or more (4)				+51			+35			—16		6

TABLE 2.—*Detailed Presentation of Basal*

Patient	Laboratory No.	Days Before Starting Iodine: 9	8	7	6	5	4	3	2	1	1	2	3	4	5	6	7	8	9
Mrs. G. H.†	1340	..	....	....	....	A	+69	+50	+47	+47	+49	....	+43	+43	+45	+42	+50	+58	....
Mr. G. C.	6711	..	....	....	A	+38	....	+42	+37	+40	+35	....	+32	....	+44	+27	+37	+36	+56
Mrs. L. P.	6723	A	....	+81	+64	....	....	....	+72	+75	+74	....	....	....	....	....	+68	+56	+61
Mrs. M. M.	6727	A	+56	....	+31	....	+39	+26	+30	+37	+29	+44	....	+27	+32	+22	+27	+26	+36
Mr. P. G.	6746	..	....	+47	....	....	+26	+28	+35	+30	+26	+21	....	+17	+22	+20	+14	+12	+17
Mr. C. F.	6752	..	A	+40	+49	+35	+34	+22	....	+30	+29	+26	+25	+30	+23	....	+11	+17	+17
Miss L. L.	6771	..	A	+57	+37	+41	+43	+31	....	+39	+42	+33	+40	+40	+43	....	+39	+43	+42
Mr. W. T.	6799	..	A	+53	....	+43	+43	+37	....	+41	+42	+38	....	+36	+33	....	+25	+28	+26
Mrs. E. P.	6885	..	....	....	A	....	+52	+42	+35	+36	+38	+39	....	+38	+28	+28	+35	+35	+34
Mr. A. C.	6894	A	+41	....	+37	+35	+30	....	+31	+32	....	+33	+23	+23	+30	+28	+26	....	+24
Mrs. M. G.	6956	..	....	....	....	+65	....	+44	+43	+43	+41	....	+29	+33	+35	+37	+35	+29	....
Mr. E. B.	6994	..	....	....	A	+40	+30	+35	+35	+31	....	+39	+40	+37	+27	+36	+40	....	+33

* A indicates admission to the hospital; S, subtotal thyroidectomy; LH, left hemithyroidectomy.
† A right hemithyroidectomy had been performed for exophthalmic goiter seven years before present admission.
‡ The time when larger doses (30 minims daily) were started.

of 0.75 Mg. of Iodine and of Much Larger Doses Given Immediately Afterward with Exophthalmic Goiter

During Administration of 0.75 Mg. of Iodine Daily, in the Form of Compound Solution								During Daily Administration of Larger Doses							
Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Time the Drop Began, Days	Drop in Basal Metabolic Rate in First 24 Hours, Points	Time Required for Maximum Drop, Days	Average Level of Basal Metabolic Rate, per Cent of Normal	Pulse Rate	Weight, Kg.	Change in Basal Metabolic Rate, Points	Length of Time Effect Was Observed, Days	Size of Dose, Minims	Total Change in Basal Metabolic Rate on All Doses	Estimated Weight of Thyroid Gland at Time of Operation, Gm.
+60	100	50.5	+12	15	0	0	0	+33	82	55.4	—27	16	30	—15	46
+48	95	53.6	+ 8	13	0	0	0	+15	77	52.9	—33	13	30	—25	..
+60	117	41.2	— 4	13	0	0	0	+14	74	41.1	—46	12	30	—50	..
+20	73	45.7	— 4	11	0	0	0	+19	70	45.5	—10	3	30	—14	34
+14	91	48.2	—19	11	2	0	4–7	+ 7	88	49.0	— 7	9	30	—26	40
+15	82	55.8	—11	10	7	0	7	+ 4	76	57.0	—11	9	30	—22	27
+20	95	35.7	+ 1	10	0	0	0	+16	79	39.7	—23	15	30	—22	39
+26	81	43.9	—13	10	6–7	0	6–7	+13	76	45.3	—13	12	30	—26	..
+32	96	49.6	— 4	9	0	0	0	+19	88	51.2	—13	10	30	—17	61
+26	72	53.8	— 5	10	0	0	0	+18	74	55.3	— 8	10	30	—13	54
+31	93	54.7	—12	12	2–3	0	2–3	+31	94	58.2	0	12	30	—12	..
+36	82	49.2	+ 3	10	0	0	0	+13	70	50.8	—23	10	30	—20	76
+35			— 4	11				+17			—18	11		—22	
+22			—13	11				+14			— 8	11		—21	

*Metabolism Data Summarized in Table 1**

Days After Starting Iodine																						
10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	31	32	
+34	+65	+68	+57	....	+57‡	....	+53	+52	+45	+43	+35	+32	....	+30	+29	+36	+39	+32	+31	+36	LH	
+45	....	+49	+42‡	+48	+46	+35	+30	....	+24	+23	+12	+13	+16	+19	....	+13 S						
+59	+57	....	+64‡	+47	+53	+47	+42	+41	....	+28	+24	+23	+17	+12	+14 S							
....	+28‡	+31	+21	+19	S																	
....	+11‡	+12	+10	+ 9	+ 8	+ 8	....	+ 8	+ 1	+ 8 S												
+15‡	+20	+ 8	....	± 0	+ 7	+10	+ 2	+ 5	+ 6 S													
+22‡	+37	+35	....	+32	+36	+28	+28	+24	+24	....	+23	+16	+15	+17	+36 S							
+25‡	+26	+23	....	+20	+31	+10	+17	+ 8	+13	....	....	+18 S										
....	+38	+28	+34	+24	+22	+22	....	+ 8	+20 S													
+24‡	+29	+30	+28	+25	....	+18	+19	+18	+19	+14	S											
+31	+32	+31‡	+30	+33	+31	....	+29	+27	+28	+34	+32	+35	+49‡S									
+36‡	+51	+41	+39	+41	....	+28	+23	+13	+12	+15	S											

* The patient suffered from acute tonsillitis with fever from the fourth day before starting iodine until the fifth day afterward.

‡ The patient worried about the operation.

cent compound solution of iodine (about 0.75 mg. of iodine)[4] was administered daily in the metabolism laboratory instead of 1 drop of the undiluted solution. It should be emphasized that the administration of iodine was not begun until the basal metabolism had reached a stationary level during rest.

Results.—The data are recorded in tables 1 and 2. It may be seen that four of the twelve patients at rest in bed showed a reduction in basal metabolism of from 11 to 19 points during the daily administration of about 0.75 mg. of iodine in the form of the compound solution; six showed no change, and two showed an increase. The average basal metabolic rate shortly after admission was plus 53 per cent; after a period of rest, it was plus 39 per cent; after reaching a level during the daily administration of about 0.75 mg. of iodine, it was plus 35 per cent, and on larger doses administered immediately afterward, it was plus 17 per cent. The corresponding figures for the four cases in which the basal metabolic rate dropped 10 or more points were plus 51, plus 35, plus 22 and plus 14 per cent, respectively (table 1).

It is of some interest that the drop in basal metabolism from rest in bed alone was almost exactly the same in all four series of hospital patients (the 6 mg.,[1] 3 mg.,[2] 1.5 mg.[3] and 0.75 mg. series).

Various types of response to the administration of 0.75 mg. daily are recorded in charts 1 to 6.

Time Required for Maximum Reduction in Basal Metabolism.—In the four patients who showed a reduction of more than 10 points, the maximum drop occurred in from two to seven days (from five to six days on the average). The average daily drop in basal metabolism in these four patients was from 2.3 to 2.8 points. In the nine patients who showed a reduction in basal metabolism of 10 or more points during the administration of large doses immediately after the small dose, the lowest level appeared in from three to twelve days, or in an average of seven days from the time the large dose was started, i. e., in the same time that is required for the basal metabolism to drop to its lowest level when large doses are given initially.

COMPARISON OF EFFECTS OF THE VARIOUS DOSES OF IODINE USED IN THE FOUR SERIES OF HOSPITAL PATIENTS

In charts 7 and 8 and in table 3 we have compared the effects on basal metabolism of administering about 6 mg.,[1] 3 mg.,[2] 1.5 mg.[3] and 0.75 mg. of iodine daily to four series of hospital patients. The per-

4. Owing to the rough method of measurement, the amount of iodine recorded as being contained in 1 drop of a 12.5 per cent compound solution of iodine is approximate, although it was always measured in the same way, using a dropper of the same size. The iodine was kept in a glass-stoppered bottle.

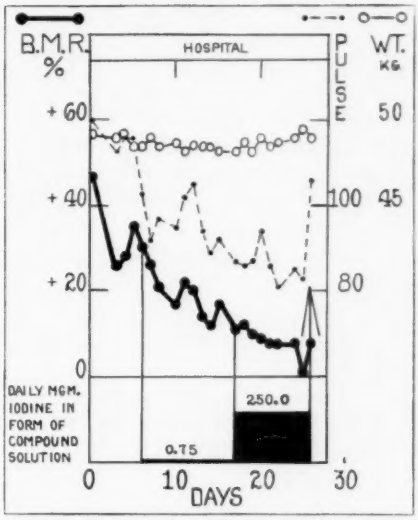

Fig. 1 (Mr. P. G., lab. no. 6746).—The greatest reduction in basal metabolism observed during the daily administration of 0.75 mg. of iodine. In this and subsequent charts, the arrow denotes subtotal thyroidectomy.

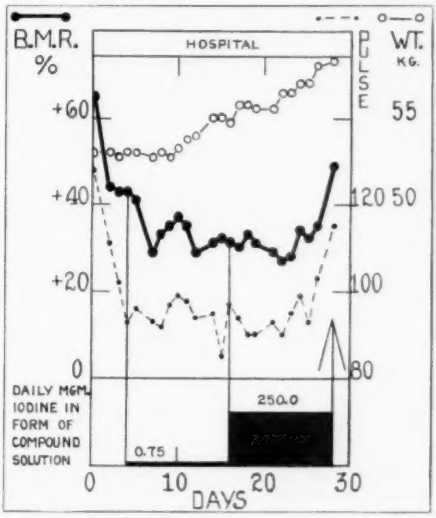

Fig. 2 (Mrs. M. G., lab. no. 6956).—Slight reduction in the basal metabolic rate during the daily administration of 0.75 mg. of iodine, and no further reduction during the immediate subsequent administration of much larger doses.

centage approach toward the average normal level of metabolism that occurred during the daily administration of 3 mg., 1.5 mg. and 0.75 mg. is roughly seven-twelfths, four-twelfths and two-twelfths, respectively, of that which occurred during the daily administration of 6 mg. (table 3); i. e., if the percentage approach toward normal be plotted against the daily dose of iodine, the points roughly fall on a straight line (chart 9).

From table 3 it may be seen that the 1.5 mg. series is the only one in which the results were definite enough to say that the small dose interfered with the effect of the large dose given immediately afterward. This phenomenon was so consistent in this series that it seems to have

TABLE 3.—*Comparison of the Effects on Basal Metabolism of the Daily Administration of About 6, 3, 1.5 and 0.75 mg. of Iodine to Hospital Patients with Exophthalmic Goiter*

		Average Basal Metabolic Rate, per Cent of Normal				During Administration of Small Dose		During Administration of All Doses	
Number Cases	Approximate Size of Small Dose, Mg. of Iodine Daily	On Admission	After Reaching a Level During Rest	After Reaching a Level During Administration of Small Dose	After Reaching a Level During Administration of Large Dose	Average Drop in Basal Metabolic Rate, Points	Percentage Approach of Basal Metabolic Rate Toward Normal Level	Average Drop in Basal Metabolic Rate, Points	Percentage Approach of Basal Metabolic Rate Toward Normal Level
14*	6.00	+62	+48	+19	+21	29	60	27	56
20	3.00	+54	+40	+26	+21	14	35	19	48
14	1.50	+62	+43	+34	+29	9	20	14	33
12	0.75	+53	+39	+35	+17	4	10	22	56

* Three cases in which large doses were not given are not considered in this table. Their omission does not alter the figures for the small dose appreciably (Thompson, Brailey, Thompson and Thorp [footnote 1, table 1]).

been more than a coincidence. The data perhaps suggest that a similar phenomenon occurred in the 3 mg. series,[2] but this does not appear to have been the case in the 0.75 mg. series. We are unable to offer any more satisfactory explanation for this difference than that already given in the third paper of this series,[3] in which certain aspects of the effects of these four doses are compared in more detail.

COMMENT

The changes observed in the basal metabolism during the daily administration of 0.75 mg. of iodine were so small that it is somewhat questionable whether they were caused by rest or by the iodine. However, since the metabolism did not drop in most cases during the daily administration of 0.75 mg., it appears that in most instances we had either secured a maximum effect from rest before this dose was started, or else the daily administration of 0.75 mg. prevented a further drop

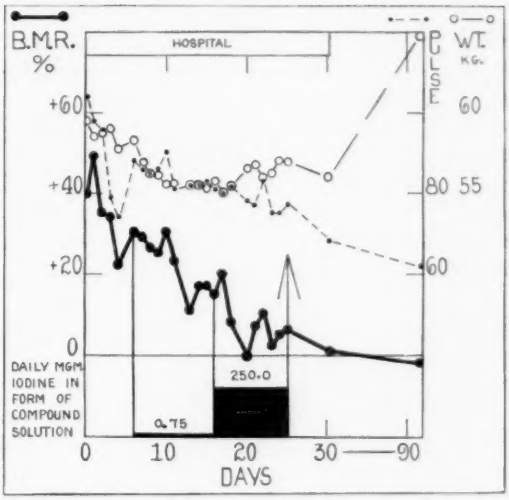

Fig. 3 (Mr. C. F., lab. no. 6752).—Slight reduction in basal metabolic rate during the daily administration of 0.75 mg. of iodine followed by a slight further reduction during the administration of much larger doses.

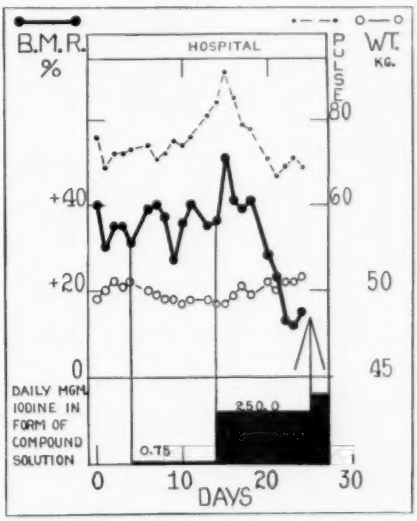

Fig. 4 (Mr. E. B., lab. no. 6994).—No reduction in basal metabolic rate during the daily administration of 0.75 mg. of iodine, followed by a well marked reduction during the administration of much larger doses.

from rest alone. In any case, the response was so small in those that showed a reduction in basal metabolism on this dose that it is impossible with present methods to measure any slight reduction that might occasionally occur during the administration of a still smaller dose.

It may now be said that whereas the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston is about 6 mg. daily, the smallest dose that will produce any reduction is a little greater than 0.75 mg. per day in about two thirds of the cases, and is probably not very much less than 0.75 mg. in the other third. Therefore, the range of effective iodine dosage in the majority of cases of exophthalmic goiter in Boston lies roughly between 0.75 and 6 mg. per day. Since the average reduction of the seven cases of the 6 mg. series that showed the smallest response [5] is greater than the average for the seven of the 1.5 mg. series that responded, and since the average reduction of the four cases of the 6 mg. series that showed the smallest response is greater than the average for the four of the 0.75 mg. series that responded, the minimum dose of iodine that will produce a maximum reduction in basal metabolism is probably rarely as low as 1.5 mg. per day. It may occasionally be as low as this, however, in spite of the presence of a considerable amount of palpable thyroid tissue.[6]

While the minimum dose that will produce a maximum reduction in basal metabolism and the smallest dose that will produce any effect vary from case to case, it is uncertain whether one is usually large when the other is large and small when the other is small or whether the magnitude of the spread in effective dosage varies markedly from case to case. It is also uncertain what the greatest minimum dose is that is ever necessary to produce a maximum reduction in basal metabolism. It is sometimes greater than 6 mg. daily.[7] Moreover, we wish to stress once again that this dose is not recommended in the routine treatment for the disease.

THE WEIGHT OF THE THYROID GLAND

The data recorded in the first three papers of this series and summarized in the third paper [3] suggested that the amount of iodine neces-

5. Throughout this study a response has arbitrarily been assumed to be a reduction of 10 or more points in the basal metabolic rate.

6. Thompson, Cohen, Thompson, Thorp and Brailey (footnote 3, table 3, case 5272).

7. Thompson, Brailey, Thompson and Thorp (footnote 1, charts 5, 6, 9 and 10). Thompson, W. O., and Thompson, P. K.: Exophthalmic Goiter: The Development of Refractoriness to Iodine, Arch. Int. Med. **48**:1 (Sept.) 1931, cases 4822 and 5168.

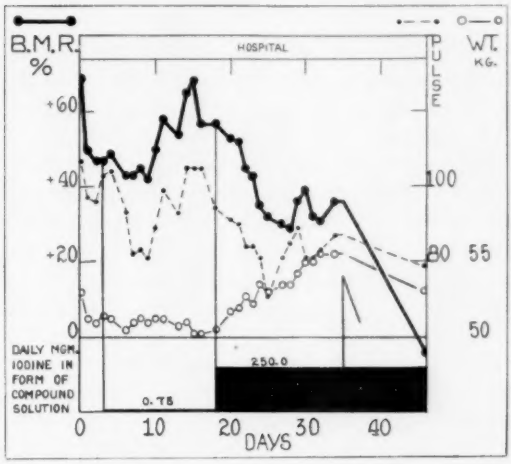

Fig. 5 (Mrs. G. H., lab. no. 1340).—Increase in basal metabolic rate and in the severity of the signs and symptoms of exophthalmic goiter during the daily administration of 0.75 mg. of iodine, followed by a decrease in both factors during the immediate subsequent administration of much larger doses.

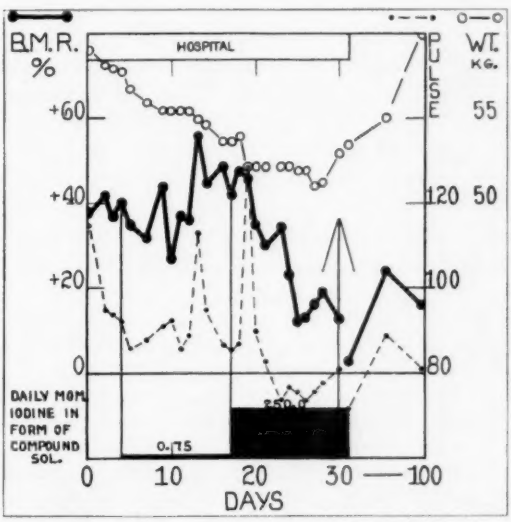

Fig. 6 (Mr. G. C., lab. no. 6711).—A slight increase in the basal metabolic rate and in the severity of signs and symptoms of exophthalmic goiter during the daily administration of 0.75 mg. of iodine, followed by a decrease in both factors during the immediate subsequent administration of much larger doses.

sary to produce a maximum reduction in basal metabolism varied with the weight of the thyroid gland. The data in this paper perhaps serve to emphasize this point. The glands, on the whole, were not large, the average weight of those weighed being only 47 Gm.; yet the average response in these particular cases was only 4 points (from plus 35 to plus 31 per cent). Using the same method of calculation as in the third paper of the series,[3] these thyroid glands would have contained: on the basis of the figures of Marine and Lenhart,[8] about 11 mg. of iodine before medication was started, and about 29 mg. after iodine was administered—a difference of 18 mg.; on the basis of the figures from the Mayo Clinic (Wilson and Kendall[9] and Weir[10]), about 9 and 24 mg., respectively—a difference of 15 mg., and on the basis of Cattell's[11] figures, about 20 and 40 mg., respectively—a difference of 20 mg. In the average time required for the response to 1.5 mg. daily to become maximum (i. e., from five to six days), not more than 4.5 mg. of iodine would have been supplied to the patients, a totally inadequate amount to cause a maximum storage of colloid. This perhaps explains not only the very slight average response, but also the small amount of reduction in basal metabolism in those who did respond. For convenience, table 6 of the third paper[3] has been brought up to date in table 4.

A comparison of the amount of iodine available for the storage of colloid on the four doses used, with the effect of these doses on the basal metabolism, suggests a rough parallelism between the two (table 5 and chart 10). Thus it appears that the percentage approach of the basal metabolism toward the normal level, the daily dose of iodine within the limits of 0.75 and 6 mg. and the amount of iodine available for the storage of colloid on doses within these limits are roughly proportional to one another.

It was pointed out in the third paper[3] that the slower rate of reduction in the basal metabolism during the daily administration of 1.5 and

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8. Marine, D., and Lenhart, C. H.: Pathological Anatomy of Exophthalmic Goiter: The Anatomical and Physiological Relations of the Thyroid Gland to the Disease; Treatment, Arch. Int. Med. **8**:265 (Sept.) 1911.

9. Wilson, L. B., and Kendall, E. C.: The Relationship of the Pathological Histology and the Iodin Compounds of the Human Thyroid, Am. J. M. Sc. **178**: 79, 1916.

10. Weir, J. F.: The Thyroxin and Tryptophane Content of the Diseased Thyroid Gland, and the Iodin Compounds in Desiccated Thyroid, Am. J. M. Sc. **169**:860, 1925.

11. Cattell, R. B.: The Pathology of Exophthalmic Goitre: A Histological and Chemical Study of the Changes Following the Administration of Iodin (Lugol's Solution), Boston M. & S. J. **192**:989, 1925.

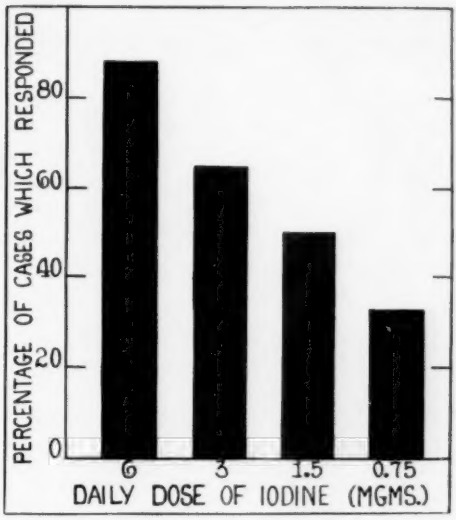

Fig. 7.—The percentage of patients who responded to each dose of iodine.

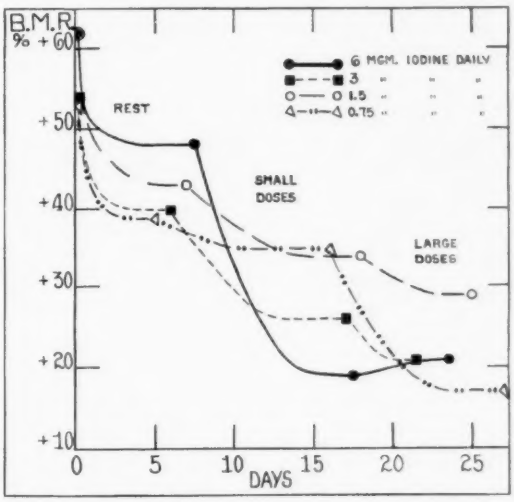

Fig. 8.—A comparison of the effects on basal metabolism of the daily administration of 6, 3, 1.5 and 0.75 mg. of iodine, respectively, to four series of hospital patients. In each case the first point is the average of the basal metabolisms shortly after admission; the second point is the average of the levels to which the metabolism fell from rest alone; the third point is the average of the levels to which the metabolism fell during the administration of small doses, and the fourth point is the average of the levels during the immediate subsequent administration of larger doses (usually about 250 mg. daily). Only those cases are considered in which the effect of larger doses was noted. The points are arbitrarily connected by curved lines, as these denote the true course of the basal metabolism more nearly than straight lines.

TABLE 4.—*Summary of Relationship Between the Estimated Iodine Capacity of the Thyroid and the Theoretical Amount of Iodine Available for Storage (of Colloid) by This Gland on the Various Doses Administered*

	Number Cases	Average Weight of Thyroid Gland, Gm.	Average Time Required for Maximum Reduction in Basal Metabolic Rate, Days	Amount of Iodine Administered in Each Case in Time Required for Maximum drop, Mg.	Possible Iodine Content of Thyroid Glands in Our Series: On Basis of Figures of Marine and Lenhart			On Basis of Mayo Clinic Figures			On Basis of Cattell's Figures			Average Basal Metabolic Rate, per Cent of Normal		Drop in Basal Metabolic Rate, Points
					Before Iodine Medication, Mg.	After Iodine Medication, Mg.	Sum of Iodine Administered and Iodine in Gland Before Medication, Mg.*	Before Iodine Medication, Mg.	After Iodine Medication, Mg.	Sum of Iodine Administered and Iodine in Gland Before Medication, Mg.*	Before Iodine Medication, Mg.	After Iodine Medication, Mg.	Sum of Iodine Administered and Iodine in Gland Before Medication, Mg.*	Before Iodine Medication	After Iodine Medication	
All 6 mg. cases in which the thyroid was weighed; all responded to iodine	8	111	7	42	25	68	67	21	57	63	47	93	89	+51	+18	33
All 3 mg. cases in which the thyroid was weighed	12	77	7	21	18	47	39	15	40	36	32	65	53	+39	+28	11
All the foregoing 3 mg. cases that responded to iodine	8	49	6	18	11	30	29	9	25	27	21	41	39	+41	+18	23
All 1.5 mg. cases in which the thyroid was weighed	11	57	5	7.5	13	35	21	11	29	19	24	48	32	+42	+33	9
All the foregoing 1.5 mg. cases in which the basal metabolic rate dropped 10 or more points on iodine	5	54	4	6.0	12	33	18	10	28	16	23	45	29	+41	+24	17
All the foregoing 1.5 mg. cases in which the basal metabolic rate dropped more than 10 points †	4	29	4	6.0	7	18	13	6	15	12	12	24	18	+40	+21	19
The 1.2 mg. case in which the thyroid was weighed	1	200	1	1.2	46	123	47	38	113	39	84	168	85	+53	+39	14
All 0.75 mg. cases in which the thyroid was weighed	8	47	5-6	4.5	11	29	16	9	24	14	20	40	25	+35	+31	4
All the foregoing 0.75 mg. cases that responded to iodine	2	33.5	6	4.5	8	21	13	6	17	11	14	28	19	+30	+15	15

* All of these figures are probably less than those recorded because, during the period of observation, the gland may lose iodine in its secretion. The amount thus lost cannot be accurately estimated at present, but it probably is not large.

† The three subdivisions of the 1.5 mg. data are made because, by including among those that responded to iodine, the one case (no. 6539) in which the thyroid weighed 154 Gm. and in which the metabolism dropped only 10 points on 1.5 mg. of iodine, the average weight of the thyroid in such cases is practically doubled (54 instead of 29 Gm.), and the difference between the iodine capacity of the gland and the theoretical amount of iodine available for storage (of colloid) is markedly increased.

3 mg. of iodine did not persist for a long enough time for the effect to equal that of administering 6 mg. daily. In other words, supplying 42 mg. of iodine in fourteen days will rarely have as much effect as supplying 42 mg. in seven days, the average rate that will produce a maximum reduction in basal metabolism in most cases of exophthalmic goiter in Boston. It thus appears that iodine must be supplied to the thyroid gland at a certain minimum rate in order for the maximum effect to occur.

TABLE 5.—*The Relation Between the Percentage Approach of the Basal Metabolism Toward the Normal Level and the Amount of Iodine Available for Storage of Colloid* *

Daily Dose of Iodine, Mg.	Number of Cases	Average Theoretical Amount of Iodine Necessary for Maximum Storage of Colloid,† Mg.	Approximate Amount of Iodine Administered in Average Time Required for Maximum Reduction in Basal Metabolic Rate, Mg.	Percentage Which the Amount of Iodine Administered Forms of the Amount Necessary for Maximum Storage of Colloid	Percentage Approach of Basal Metabolic Rate Toward the Normal Level
6	8	42	42	100	65
3	12	29	21	72	28
1.5	11	21	7.5	34	21
0.75	8	18	4.5	25	11

* This table applies only to cases in which the thyroid glands were weighed. Thus the figures in the last column are slightly different from those in the corresponding column of table 3.

† The iodine content of the thyroid after medication minus the iodine content before medication was started. In obtaining these figures, the amounts estimated from the figures of Marine and Lenhart, the Mayo Clinic and Cattell in table 4 were averaged.

PATIENTS SHOWING A RISE IN BASAL METABOLISM DURING THE ADMINISTRATION OF SMALL DOSES OF IODINE, FOLLOWED BY A DROP DURING THE IMMEDIATE SUBSEQUENT ADMINISTRATION OF LARGE DOSES

There were five cases that showed an increase in basal metabolism during the administration of from 0.75 to 3 mg. of iodine daily, followed by a decrease during the immediate subsequent administration of much larger doses (table 6). In view of the level to which the basal metabolism fell during rest, the drop on all doses in these five cases was only 16 points (from plus 44 to plus 28 per cent), i. e., only about half as much as would be expected from initially giving large doses. Considering only the drop that occurred during the administration of large doses, it was fairly well marked (from plus 60 to plus 28 per cent), although the approach toward normal was less than that noted in initially giving 6 mg. daily to the first series of hospital patients. In these cases, therefore, the small dose did in some way prevent the patient from receiving the maximum benefit from iodine. Since this occurred in 10 per cent of the cases in the 3 mg.,[2] 1.5 mg.[3] and 0.75 mg.

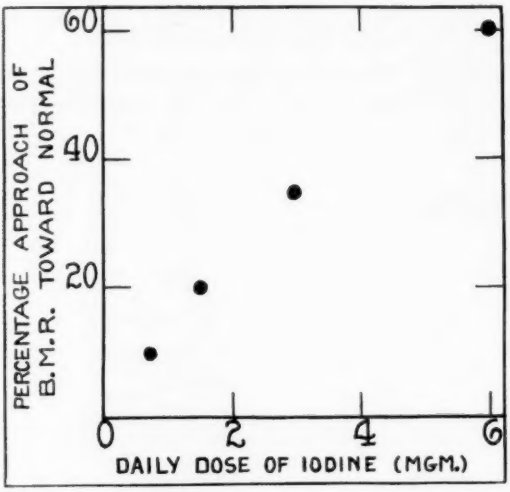

Fig. 9.—The relation between the dose of iodine and the percentage approach of the basal metabolism toward the normal level.

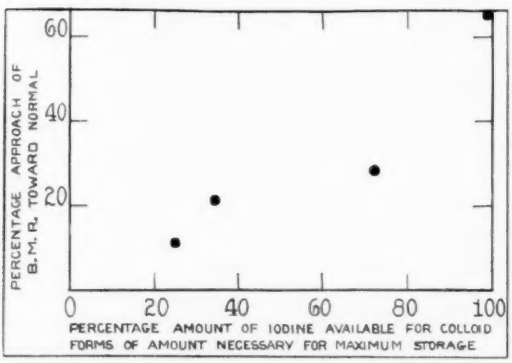

Fig. 10.—The relation between the percentage approach of the basal metabolism toward the normal level and the amount of iodine available for storage of colloid (see table 5).

series, since the rise on small doses was preceded by a drop with rest and was followed by a drop during the administration of large doses given immediately afterward, and since all these changes occurred in so short a time, it can scarcely be regarded as a coincidence that the basal metabolism rose during the administration of small doses. The data in this paper thus serve to support a conclusion previously reached, viz., that in a certain proportion of cases the reaction to iodine is a reversible one. In such cases it appears that if the amount of iodine administered is inadequate to initate the change in the thyroid gland that is associated with a reduction in basal metabolism, it is utilized to

TABLE 6.—*Patients Showing a Rise in Basal Metabolism During the Administration of Small Doses of Iodine, Followed by a Drop During the Immediate Subsequent Administration of Large Doses*

Patient	Laboratory Number	Basal Metabolic Rate on Admission	Level of Basal Metabolic Rate During Rest	Level to Which Basal Metabolic Rate Rose During Administration of Small Doses of Iodine	Level to Which Basal Metabolic Rate Dropped During Administration of Large Doses of Iodine	Approximate Size of Small Dose of Iodine, Mg. Daily
Mrs. G. H.	1340	+69	+48	+60	+33	0.75
Mr. G. C.	6711	+38	+40	+48	+15	0.75
Mrs. M. S.	6586	+98	+60	+68	+44	1.50
Mr. T. B.	6135	+32	+25	+52	+27	3.00
Mr. J. B.	6264	+48	+47	+70	+23	3.00
Average		+57	+44	+60	+28	

increase the output of the thyroid secretion, whereas if it is adequate to initiate this change, the output is diminished.

We wish to emphasize once again that the conclusions here reached can at present be said to apply only to the place from which the patients came, viz., Boston and vicinity.

SUMMARY

During the daily administration of about 0.75 mg. of iodine in the form of the compound solution to twelve unselected hospital patients with exophthalmic goiter, four showed a reduction in basal metabolism of from 11 to 19 points, six showed no change and two showed an increase.

Whereas only 33 per cent of the patients showed a reduction in basal metabolism of 10 points or more during the daily administration of 0.75 mg., 50 per cent showed a reduction during the daily administration of 1.5 mg., 65 per cent during the daily administration of 3 mg., and 88 per cent during the daily administration of 6 mg.

The administration of about 0.75 mg. a day caused an average reduction in basal metabolism of 4 points (from plus 39 to plus 35 per cent) as compared with 9 points (from plus 43 to plus 34 per cent) for 1.5 mg., 14 points (from plus 40 to plus 26 per cent) for 3 mg., and 27 points (from plus 36 to plus 19 per cent) for 6 mg.

Whereas the minimum amount of iodine that will produce a maximum reduction in basal metabolism in most hospital patients with exophthalmic goiter in Boston is about 6 mg. per day, the smallest amount that will produce any effect is greater than 0.75 mg. per day in about two thirds of the cases, and is probably not much less than 0.75 mg. per day in the other third.

Within these limits of dosage there appears to be roughly a linear relationship between the percentage approach of the basal metabolism toward the normal level and the dose of iodine.

It also appears that within these limits of dosage the reduction in basal metabolism is roughly proportional to the amount of iodine available for the storage of colloid.

In five of forty-six patients who received from 0.75 to 3 mg. of iodine daily, the reaction to iodine appeared to be reversible; i. e., the basal metabolism rose during the administration of the small dose and fell during the immediate subsequent administration of a much larger dose.

Iodine must be supplied to the thyroid gland at a certain minimum rate in order for the maximum effect to occur.

CINCHOPHEN POISONING

AN ATTEMPT TO PRODUCE TOXIC CIRRHOSIS OF THE LIVER IN RATS *

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CLEVELAND

In a previous paper [1] two cases of toxic cirrhosis were described that were observed clinically and examined at autopsy in the Cleveland City Hospital. Reports of many cases have since then appeared in the literature; cinchophen and its allies may now be regarded as drugs of considerable potential toxicity. Nevertheless, it remains true that cinchophen is used extensively without any apparent ill effects. It is, therefore, of considerable importance that the mechanism of the drug's toxic action be explained.

EXPERIMENTS

Adult albino rats were used in these experiments. They were fed dried whole milk, whole wheat flour, calcium carbonate, sodium chloride (Sherman's diet B) and weekly additions of meat and greens. In many of the rats infections of the upper and lower respiratory tracts developed, such as purulent bronchitis, pneumonia with atelectasis and disease of the middle ear, which were found with equal frequency among the controls.

The lethal dose of a single parenteral administration of cinchophen was first determined. Four rats weighing about 300 Gm. were given subcutaneously from 1 to 2 Gm. per kilogram of body weight of a suspension of the drug in acacia. All the animals died within twenty-four hours and exhibited profound disturbances of the central nervous system, such as listlessness, interference with the preservation of equilibrium and generalized convulsions, a tremendous diuresis and severe dyspnea. Microscopic examination of the organs, however, did not permit these symptoms to be ascribed to any specific toxic effect. The slides showed uniformly a poor staining quality of the tissue and extreme degeneration of the parenchyma of the liver, kidney and spleen. The necrotic cells exhibited a peculiar circumnuclear edema. The lymphatic tissue everywhere appeared to be depleted of cells.

* Submitted for publication, June 22, 1931.

* From the Institute of Pathology and the Department of Pediatrics, Western Reserve University.

1. Reichle, H. S.: Toxic Cirrhosis of Liver Due to Cinchophen, Arch. Int. Med. **44**:281 (Aug.) 1929.

These results are ascribed to a very gross form of poisoning, probably due to the acidity of the drug.

In the second experiment, the dosage of the drug was reduced and only from 0.2 to 0.5 Gm. per kilogram of weight was administered in the same manner. The injections were repeated daily for eight days. Dyspnea and diuresis were again observed. The animals lost weight, their fur was ruffled and disorganized, and the penis projected from the prepuce. However, there were no specific changes; the parenchymatous organs were in a state of severe cloudy swelling, but the nuclei were well preserved. The liver, it is true, showed many focal necroses, circular areas that stained a uniform pink and that contained densely staining nuclei, apparently belonging to cells of the reticuloendothelial system. Little importance is attached to these changes, since they are found in many toxic conditions in the rat, and particularly because rat 7, which was killed seventeen days after the last injection, had a normal histologic structure of the liver. In no case was there any evidence of connective tissue proliferation. Evidently, therefore, the changes observed in the rats killed during the course of the injections had been repaired by a restitutio ad integrum. The striking feature of the toxic cirrhosis caused by cinchophen is the incapacity of the organ to restore its parenchyma. There are destruction of parenchyma, proliferation of connective tissue and disorganization of the natural architecture. The severe nature of the hepatic injury has recently been well described by Beaver and Robertson.[2]

A subsequent attempt to develop specific damage by the use of the lowest dose (0.2 Gm. per kilogram) over a longer period of time (thirteen injections) also failed. Again dyspnea was observed, there were periods of excitement, and even collapse occurred immediately after an injection. After the last dose, the experimental rats showed great uneasiness, the respirations were deep and panting, the gait was a wabble, and the head and anterior extremities were dragged along the floor. The animals sought the corners of their cages. Microscopic examination, however, again revealed nothing but the changes already described.

The parenteral administration of the drug having failed, the enteral route was next tried on the chance that the drug might by this path exert its full toxic action directly and immediately on the liver. Following a suggestion of Dr. Paul Klemperer of Mount Sinai Hospital, New York, this organ was first deprived of its store of glycogen, since

2. Beaver, D. C., and Robertson, H. E.: The Specific Character of Toxic Cirrhosis as Observed in Cinchophen Poisoning, Proc. Staff Meet., Mayo Clin. **6**:216, 1931.

many researches (Fischler [3]) have shown the importance of carbohydrate in the protection of the liver against toxic agents of many different types. The rats were starved for five days. A control rat killed at this time demonstrated that all glycogen that can be obtained by hot alkaline extraction from the fresh liver had been removed. The animals, whose weights varied from 165 to 210 Gm., were given 20 mg. of cinchophen by mouth three times on the first day, and thereafter 4 mg. twice a day for ten days. A second period of starvation of twenty-four hours was followed by two days on which 60 mg. was administered each day, and from then on 10 mg. was given twice daily. The drug was administered suspended in olive oil. The animals were killed at the close of the experiment, after having taken 1,380 mg. each in seventy-two days. The results of histologic examination were entirely negative. In one rat uremia developed on the thirty-third day (after the administration of 576 mg. of cinchophen). Autopsy revealed an extraordinary degeneration of the cortical portion of the kidneys; the glomeruli had largely disappeared and were replaced by fibrous masses, which were in part calcified. The liver showed no changes that could not be considered a part of the uremic toxicosis. This was the only case of severe chronic organic disease not due to infection that was encountered. According to Jaffe,[4] such renal degenerative disease occurs in the rat under laboratory conditions and is of unknown etiology. A second experiment of the same type as the preceding one, in which four rats were given 880 mg. of cinchophen per os in thirty-one doses, and three rats the same amount of neocinchophen, resulted in nothing more than a severe cloudy swelling of the liver. Neocinchophen was added in this experiment to determine whether this ester of cinchophen, which is regarded as entirely innocuous, might not possess the same toxic properties as cinchophen.

Further experiments followed the principle of a double hepatic injury. The liver of the experimental rat was injured with chloroform, and cinchophen was then administered per os. In one experiment the chloroform was given by inhalation to complete narcosis on four successive days. Seven rats were then given 20 mg. of cinchophen three times a day for twelve days. At autopsy no gross changes were seen. Unfortunately, the specimens were lost, so no microscopic

3. Fischler, F.: Ueber Probleme des Kohlenhydratstoffwechsels mit besonderer Berücksichtigung der Rolle der Leber, Deutsche med. Wchnschr. **55**:605, 1929; Zur Chemie und zur therapeutischen Wirkung des Traubenzuckers, München. med. Wchnschr. **75**:1541, 1928; Traubenzucker als Therapeutikum, ibid. **76**:791, 1929.

4. Jaffe, R.: Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere, Berlin, Julius Springer, 1931.

report can be given. In the second experiment of this type, the chloroform was given subcutaneously in solution with olive oil. It was found that this method was the least dangerous and the most accurate in dosage. The animals appeared to suffer no pain and were quite drowsy. A total of from 0.33 to 0.75 Gm. of chloroform was given in three days. Postmortem examination of one animal which had received 0.57 Gm. in four days showed the presence of a large fatty, hemorrhagic, friable liver. The remaining rats were then given 300 mg. of cinchophen in ten days and were killed five days after the last dose. Histologic examination revealed no pathologic changes of importance. These experiments show that, at least in the rat, it is not possible, by the ordinary methods, to reproduce the toxic cirrhosis characteristic of cinchophen poisoning.

In a previous article [1] I stated "that there is little doubt but that natural idiosyncrasy may be of importance. . . . It is also thought that idiosyncrasy may be artificially induced. Worster-Drought's [5] patient, after having taken 370 grains in twelve days developed urticaria, which disappeared when the medication was stopped. One dose of 7.5 grains administered three weeks subsequently brought on urticaria, gastro-intestinal disturbance and jaundice, which lasted ten days." Evans,[6] Anderson and Teter [7] and Barron [8] reported the same experience. Barron's case showed a particularly exquisite manifestation of hypersensitiveness which occurred in a patient who had had previous medication with cinchophen. Immediately following the renewal of the drug a severe reaction occurred, which repeated itself on a third attempt to use cinchophen. Barron called attention to the patient described by Boots and Miller who reacted adversely to the first administration of cinchophen. Schwann [9] used atophanyl, a cinchophen preparation for intravenous use. He observed severe prostration after the first injection in one patient. There were anginal pains, vasomotor disturbances, unconsciousness, cyanosis and profuse sweating. In another case the untoward reaction was seen after the third injection. The patient became restless, and a chill, angioneurotic edema of the face and severe urticaria developed. It is true that not all cases show these classic symptoms, nor is the course always char-

5. Worster-Drought, C.: Atophan Poisoning, Brit. M. J. **1**:148 (Jan. 27) 1923.

6. Evans, Geoffrey: Discussion, Brit. M. J. **2**:689 (Oct. 16) 1926.

7. Anderson, S. D., and Teter, D. P.: Acute Yellow Atrophy of the Liver Following Administration of Oxyl Iodide, J. A. M. A. **93**:93 (July 13) 1929.

8. Barron, M.: Cinchophen Poisoning, J. A. M. A. **82**:2010 (June 21) 1924.

9. Schwann, W.: Unerwünschte Atophanwirkung., Klin. Wchnschr. **3**:935, 1924.

acteristic. There are probably several different reasons for this. The drug is often continued long after the toxic symptoms have manifested themselves (as in my own cases [1] 1 and 2). Again, not always do all of the most striking symptoms of hypersensitiveness appear. There are, moreover, two types of sensitivity: In the one, the patient is primarily sensitive (Boots and Miller's case, cited by Barron [8]); in the other, the sensitivity is probably acquired (Worster-Drought [5]). It is particularly the latter type that is most interesting, since it shows a close relationship of this sensitivity to others which, because of the therapeutic importance of the drugs involved, have been more closely studied. The reactions to arsphenamine and sensitivity to nirvanol (phenyl-ethyl-hydantoin) are examples.

Nirvanol, which was orginally used as a sedative and hypnotic, was abandoned because of the rashes that frequently followed its use. The German pediatricians observed a uniformity in the course of the rash due to nirvanol, or, more properly, the sickness due to this medication. In a large percentage of the patients who were treated with this drug a severe morbilliform eruption occurred from the seventh to fourteenth day of administration. Following this reaction, the patients (the condition was chorea) showed remarkable improvement. Since then these observations have been verified by many investigators. A discussion of the results is given in the paper by Pilcher and Gerstenberger.[10] It is important to note that the rash is only the external, and not a necessary, manifestation of a general reaction of the body to the drug. This is characterized by fever and changes in the metabolism, which are independent of the pyrexia (Beck [11]), relative and absolute lymphocytosis and eosinophilia.

It appears that the reaction to cinchophen is probably of the same type. The symptoms are strikingly allergic: a rash, often urticarial, edema, vasomotor changes, sweating, disturbance of the oxygen exchange and vomiting. The free interval, the frequency of "safe" previous medication, the appearance of the symptoms after the drug has been stopped, which reminds one of serum sickness, the lack of premonitory symptoms and the acuteness of the onset are suggestive of a hypersensitive state. The toxicity does not depend on dosage. Some of the patients received small amounts, others large doses over long periods of time. In all cases the onset is relatively acute. It is beyond the scope of this report to enter into a discussion of the nature of this sensitivity. In my opinion, the reactions fall into the realm

10. Pilcher, J. D., and Gerstenberger, H. J.: Treatment of Chorea with Phenyl-Ethyl-Hydantoin, Am. J. Dis. Child. **40**:1239 (Dec.) 1930.

11. Beck, O.: Ueber Veränderungen des kindlichen Stoffwechsels bei Nirvanol-Zufuhr, Monatschr. f. Kinderh. **45**:486, 1930.

of the anaphylactoid (Hanzlik and Karsner [12]). Karsner [13] enumerated the following symptoms: "increased reflex excitability, rapid respiration and dyspnea, sneezing, retching, jerky spasms, slowing or acceleration of the heart, trembling, expulsion of urine, cyanosis, pupillary relaxation, convulsions and death with large doses"—all of which have also been described in cases of cinchophen poisoning. Some of these symptoms were observed by me in the course of the parenteral administration of the drug to rats. With animals more susceptible to allergic manifestations it might have been possible to obtain more convincing evidence. It is also possible that cinchophen poisoning is precipitated by a reaction of various antibodies with this nonantigenic compound, as Landsteiner [14] has proved for metanilic acid, para-arsenilic acid and *p*-amino benzoic acid. Following this thought, we may perhaps conceive of a similar mechanism by which the drug combines with a protein of the subject to form a complex compound of protein and nonprotein radicals. As Landsteiner has shown, the nonprotein radicals can react with the immune serum of animals treated with the entire compound and of themselves saturate the specific antibody. Perhaps in vivo they might cause such hypersensitive conditions as are observed in phenyl-ethyl-hydantoin and cinchophen poisonings.

CONCLUSIONS

Subcutaneous administration of cinchophen in single doses of 1 Gm. per kilogram of body weight killed rats within twenty-four hours. Continued parenteral administration of smaller doses (0.2 Gm. per kilogram) did not cause death, but after the last two injections, the rats displayed symptoms that may possibly be regarded as expressions of hypersensitiveness. Feeding of cinchophen in doses of approximately 20 mg. a day to rats when the livers had been depleted of glycogen by starvation or injured by chloroform did not induce cirrhosis. No characteristic changes in the histologic appearance of the organs were found on postmortem examination.

A review of the histories of cases of reaction to cinchophen suggests that its cause may be found either in a natural hypersensitiveness or in the development of a hypersensitive state.

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12. Hanzlik, P. J., and Karsner, H. T.: Anaphylactoid Phenomena from Intravenous Administration of Various Colloids, Arsenicals and Other Agents, J. Pharmacol. & Exper. Therap. **14**:379 (Jan.) 1920; Effect of Various Colloids and Other Agents Which Produce Anaphylactoid Phenomena on Bronchi of Perfused Lungs, ibid. **14**:449 (Feb.) 1920.

13. Karsner, H. T.: Anaphylaxis and Anaphylactoid Reactions, in Jordan, E. O., and Falk, I. S.: The Newer Knowledge of Bacteriology and Immunology, Chicago, University of Chicago Press, 1928, p. 985.

14. Landsteiner, K.: Biochem. Ztschr. **93**:106, 1919; **104**:280, 1920.

BLOOD SUGAR IN MAN FOLLOWING THE RECTAL ADMINISTRATION OF DEXTROSE *

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The dextrose retention enema is such a common clinical procedure, and the impression that considerable amounts of dextrose are absorbed after rectal administration is so well established in spite of the conflicting nature of the experimental data submitted in evidence that we considered the problem worthy of further investigation.

Clendening [1] recommended such enemas, quoting Edsall to the effect that nine tenths of the carbohydrate injected is "taken up by the rectum." Sollmann [2] stated that dextrose is "absorbed effectively from nutrient enemas." Lütje treated diabetic acidosis by rectal injections of sugar, and Joslin [3] noted that as long ago as 1904, Arnheim reported that acetonuria of diabetic patients was diminished after the rectal administration of sugar solutions. Tallerman [4] reported an elevation of the blood sugar curve in some of his cases. Carpenter [5] stated that the absorption may be as much as 90 per cent of the dextrose administered. Varela and Rubino [6] reported glycosuria in seven of seventeen cases following the administration of a sugar solution by means of a rectal drip. Hari and von Halasz [7] approached the problem through a study of the respiratory gases and reported a rise of the respiratory quotient after rectal administration of dextrose. Carpenter [5] reported similar results, but both he and Pressman [8] warned against accepting a rise in the respiratory quotient as necessarily indicating that a considerable amount of sugar has been absorbed.

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* From the Department of Physiology, Columbia University.

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4. Tallerman, K. H.: Quart. J. Med. **13**:356, 1920.

5. Carpenter, T. M.: Human Metabolism with Enemata of Alcohol, Dextrose and Levulose, Publ. Carnegie Inst., Washington, D. C., Dec., 1925.

6. Varela and Rubino: Med. Klin. **26**:831, 1922.

7. Hari, P., and von Halasz, A.: Biochem. Ztschr. **88**:337, 1918.

8. Pressman, J.: Am. J. M. Sc. **179**:520, 1930.

Levi [9] seems to believe that the rectal administration of dextrose is of little practical value. Mekie and Miller [10] found no consistent change in blood sugar value. Franke and Wagner [11] reported varying results with three dogs. Pressman, and Rubino and Varela [12] reported a drop in the blood sugar curve.

The amount of dextrose returned in the stools after the enemas have been retained for some time has been investigated by many observers. Pressman [8] reported about 25 per cent recovered after four hours. McNealy and Willems [13] were able to recover about 98 per cent from the colon of dogs after one hour. Varela and Rubino [6] recovered about 60 per cent. Various percentages are reported by other authors, and while there appears to be no agreement as to the actual amount that may be recovered after a definite period, all who have investigated this aspect of the problem have reported substantial returns.

That the bacterial flora of the large bowel plays no inconsiderable part in the problem has been shown by Bingel (quoted by Pressman [8]), who was able to cause the disappearance of about 30 per cent of the sugar by incubating it with feces for five hours. Pressman [8] himself reported the loss of 90 per cent after seven hours' incubation.

The great diversity of results that appear is undoubtedly bound up with the widely differing material and methods that have been used in attacking the problem. The subjects have been sick men, well men, anesthetized men, men who had just recovered from an operation and anesthetized dogs. The sugar solutions have been administered as drip or retention enemas, and in the latter event the volume injected has varied from 180 to 600 cc., while the concentration has been almost anything from an isotonic to a 50 per cent solution. In few instances is any specific mention made of the brand of dextrose used. The methods employed for the determination of the blood sugar have varied widely. Finally, in spite of the rather voluminous literature on the subjects, there has been only a comparatively small number of actual cases reported.

In the belief that a significant norm would be of value not only in forming an opinion but as an aid to future work, we have approached the problem from a statistical standpoint. We felt that there was nothing in the previous work to prove that a small constant deviation in the blood sugar curve might not have been overlooked. Our approach has been physiologic rather than clinical. We wish to emphasize that

9. Levi, D.: Brit. J. Surg. **15**:282, 1927.
10. Mekie, E., and Miller, H.: Brit. M. J. **1**:244 (Feb. 9) 1929.
11. Franke, W., and Wagner, R. J.: J. Metab. Research **6**:375, 1924.
12. Rubino and Varela: Klin. Wchnschr. **1**:2370, 1922.
13. McNealy, R. W., and Willems, J. D.: Surg., Gynec. & Obst. **49**:794, 1929.

we are concerned primarily with the blood sugar curve as such, and to point out that variations in that curve, or the lack of them, or variations in the respiratory quotient, cannot be definitely correlated with the absorption of specific amounts of sugar.

According to one of us (Dr. Scott [14]) our first few results showed such a deviation as to indicate that at least fifty cases would have to be studied before a definite conclusion would be warranted.

EXPERIMENTAL DATA

Our subjects were healthy, first year medical students. They reported to the laboratory after a twelve hour fast and were given a preliminary enema of 200 cc. of warm tap water. This was passed at once, and the blood sugar concentration during fasting was determined. The subjects were then given solutions of dextrose of varying concentrations by rectum, which they retained for two or three hours. At the end of this time the enemas were returned, and their sugar

TABLE 1.—*Blood Sugar per Hundred Cubic Centimeters at Varying Periods After the Administration of 200 Cc. of 10 Per Cent Dextrose Solution by Rectum*

Body Weight, Pounds	Fasting	½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	3 Hr.	Stool Return, Gm.
155	114	102	113	...	121	...	100	...
170	118	117	110	107	122	117	122	1.7
...	106	103	...	108	113	...	114	...
150	104	105	99	...	106	111	...	2.3
115	118	101	90	94	112	100	...	6.0
145	114	99	94	97	97	97	...	...
184	114	111	107	106	107	110	...	2.0
140	103	95	91	96	99	93	...	5.2
185	111	105	105	103	98	103	...	5.3
Averages.....	111	104	101	102	108	105	112	

content was found by a modification of the Benedict quantitative method for determining urinary sugar. About one half of the subjects were given additional enemas of tap water at the close of the experiment to wash out the rectum, but these showed no significant increase in the amount of dextrose returned over that obtained from those in whom this process was omitted. During the time the enema was retained, samples of blood were drawn from veins in the arm at specified intervals and their sugar content determined by the method of Shaffer and Hartmann.[15] The sugar values were calculated from the table [16] of Duggan and one of us (Dr. Scott). The determinations were made in duplicate, the values reported being the averages of the duplicate determinations. The blank spaces on the charts represent points at which, for various reasons, such as marked disagreement between two tubes or difficulties in the class schedules of the student subjects, the figures could not be obtained. About 10 per cent of the subjects reclined on a bed during the entire period of the experiment; the remainder went about the building to their classes, returning at stated intervals for the withdrawal of samples of blood.

14. Scott, E. L.: J. Biol. Chem. **73**:81, 1927.
15. Shaffer, P. A., and Hartmann, A. F.: J. Biol. Chem. **45**:365 (Jan.) 1921.
16. Duggan, W. F., and Scott, E. L.: J. Biol. Chem. **67**:287, 1926.

We attempted to use moderately high concentrations in a few cases. These solutions caused so much discomfort, such as pain, urgent desire to defecate and nausea, that we were forced to abandon them in favor of more dilute solutions. Four hundred cubic centimeters of a 10 per cent solution could be retained without much annoyance.

To each of a group of four subjects, 200 cc. of 10 per cent dextrose solution was given by mouth. The blood sugar curve for this group showed the usual

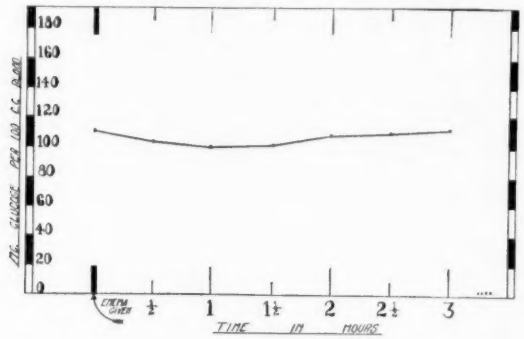

Chart 1.—Graph of the results of the administration of 200 cc. of 10 per cent dextrose per rectum.

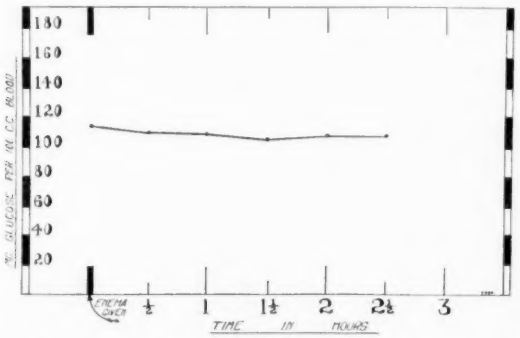

Chart 2.—Graph of the results of the administration of 400 cc. of 10 per cent dextrose per rectum.

alimentary rise at the end of thirty minutes and one hour. Three subjects were given 180 cc. of 15 per cent solution by rectum, and no significant deviation from the fasting level was noted in their blood sugar curves over a period of two and one-half hours. Three subjects, who were given 180 cc. of 30 per cent dextrose solution, were unable to retain the enema longer than half an hour. At that time, their blood showed no significant change in its sugar level. Nine subjects were given 200 c. of a 10 per cent dextrose solution by rectum. The arithmetical means for this group show a drop of 10 mg. per cent at one hour (table 1, chart 1). In

view of the small number in this series and the relatively large deviations, we do not consider that at present a definite significance can be attached to this drop.

Fifty subjects were given 400 cc. of a 10 per cent solution of dextrose by rectum (table 2, chart 2). The arithmetical mean for this group shows a gradual

TABLE 2.—*Blood Sugar After the Administration of 400 Cc. of 10 per Cent Dextrose Solution by Rectum*

Body Weight, Pounds	Fasting	½ Hr.	1 Hr.	1½ Hr.	2 Hr.	2½ Hr.	Stool Return, Gm.
155	103	102	96	93	97	94	11.1
160	107	91	97	96	94	108	5.0
140	92	103	99	98	105	102	9.9
156	110	103	110	97	97	99	8.6
124	97	87	99	94	94	93	10.1
180	118	113	118	...	115	...	19.0
...	122	117	116	...	121	...	21.0
145	125	116	...	...	...	...	3.5
125	107	99	96	...	103	...	21.0
...	117	119	120	...	119	...	18.0
...	...	...	105	...	105	...	8.6
148	107	110	105	...	103	...	15.0
...	125	137	123	...	116	...	10.0
160	110	114	101	...	109	...	18.0
155	125	118	125	...	118	...	21.0
130	86	87	84	...	84	...	17.0
165	124	110	105	...	105	...	19.0
155	101	105	104	...	99	...	8.0
170	110	107	108	...	108	...	13.0
140	102	97	102	92	99	103	32.0
160	101	...	107	108	108	110	3.0
165	100	108	96	105	93	104	15.0
180	123	113	123	117	113	112	18.0
125	119	123	119	114	113	115	....
180	118	117	108	109	102	103	17.0
145	110	102	103	102	113	102	9.0
180	130	117	118	118	116	111	1.0
134	135	128	118	113	116	121	13.0
196	120	115	115	116	114	119	15.0
113	155	120	96	106	105	135	0.6
135	106	106	103	108	112	109	22.0
160	124	118	112	121	121	120	2.0
180	111	75	119	115	...	110	19.0
155	128	131	125	121	120	125	11.0
138	105	109	113	108	108	104	4.7
140	118	115	112	107	107	114	1.8
135	107	97	109	99	107	105	2.0
139	...	108	106	101	101	100	0.8
155	103	99	108	97	...	98	5.7
162	107	112	102	105	...	98	14.0
165	117	110	...	114	112	...	....
138	103	105	102	100	100	100	8.0
200	106	99	102	104	108	107	10.2
145	104	107	102	102	102	97	7.1
155	119	118	124	109	124	124	15.8
180	106	...	98	99	109	104	15.8
160	119	109	110	105	112	104	18.0
147	110	112	107	96	105	103	19.5
147	107	99	103	105	99	101	5.3
135	125	110	102	103	104	113	9.8
Number of determinations	48	47	48	36	46	35	48
Average.....	113.0	108.9	107.8	105.5	107.3	107.4	
e*.....	13.8	11.5	9.4	8.0	8.6	9.2	
e_M*.....	1.7	1.7	1.3	1.3	1.3	1.8	

* Scott (footnote 14).

fall in the blood sugar curve; the lowest point is reached one and one-half hours after the administration of the dextrose. This point is 7.5 mg. per hundred cubic centimeters below the fasting level. The values for e^{14} are, however, of such an order that we cannot say that the drop is definitely significant.

The figures for the dextrose in the returned enemas are highly variable; it is worthy of note, however, that in thirty-one of fifty-four cases, one quarter or more of the administered dextrose was returned, and in five instances, over one-half was returned.

The sugar that was not recovered in the stools may possibly have risen higher in the large bowel because of antiperistalsis or for some other reason, there to be retained for a slow absorption, partial destruction by fermentation or a later return. A certain amount may have entered the blood stream at a rate too slow to elevate the blood sugar concentration significantly. The drop in the curve, if in fact there is an actual drop, might be taken to indicate that there has been absorption of an amount sufficient to stimulate the outpouring of insulin.

CONCLUSIONS

1. It has not been possible to demonstrate a rise in the blood sugar curve as a result of administering dextrose in retention enemas.

2. The slight drop that our curves show may be due to a stimulation of pancreatic activity brought about by the absorption of a slight amount of dextrose, or, more probably, to chance variation.

3. A variable and frequently considerable amount of dextrose administered by enema may be recovered from the stools after two and one-half hours.

VISCEROCARDIAC REFLEXES

AN EXPERIMENTAL STUDY IN FROGS AND DOGS *

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The impression that visceral excitation may produce reflex alteration of cardiac activity is rapidly gaining ground in the clinical literature. Occasionally, even the death of the patient has been attributed to such a reflex disturbance. Of all the viscera that may influence the heart reflexly, the gallbladder and the biliary passages have been most suspected. Osler [1] and Albutt [2] cited instances in which patients died during gallstone colic and ascribed the death to reflex vagal inhibition. Others [3] have commented on the relation of cardiac arrhythmia to gallstone colic. Several writers [4] have reported a series of cases showing that myocarditis and cholecystitis are so frequently associated that some meaning for the association probably exists. Babcock,[5] Mayo,[6] Strauss and Hamburger [7] have reported cases of cardiac disorders in which improvement occurred after operation was performed on the biliary tract.

That cardiac irregularities may be induced reflexly from visceral excitation is supported by certain experimental evidence. The well known Goltz experiment, in which tapping of the viscera in the frog

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* From the Department of Physiology and Pharmacology, Northwestern University Medical School.

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2. Albutt, C., cited by Babcock (reference 1).

3. Reisman, D.: The Development of Cardiac Murmurs During Attacks of Biliary Colic, J. A. M. A. **48**:1589 (May 11) 1907. Külbs: Handbuch der inneren Medizin, Berlin, Julius Springer, 1914, vol. 2, p. 1239. Umber: ibid. vol. 3, pt. 1, p. 115. Lichty, M. J.: Ohio State M. J. **11**:779, 1915.

4. Schwartz, M., and Herman, A.: Ann. Clin. Med. **4**:783, 1931. Willius, F. A., and Fitzpatrick, J. M.: J. Iowa M. Soc. **15**:589, 1925. Leech, C. B.: New England M. J. **26**:1318, 1929.

5. Babcock (reference 1). The Diagnosis of Chronic Cholecystitis Complicating Cardiac Lesions, J. A. M. A. **73**:1929 (Dec. 27) 1919.

6. Mayo, W. J.: Illinois M. J. **45**:33, 1924.

7. Strauss, D. G., and Hamburger, W. W.: The Significance of Cardiac Irregularities, J. A. M. A. **82**:706 (March 1) 1924.

causes reflex slowing of the heart, is the oldest evidence bearing on this question. More recently, Carlson and Luckhardt [8] stated as a result of their experiments that "in the frog stimulation of the lungs, the gastro-intestinal tract and genito-urinary tract causes reflex cardiac inhibition. In curarized preparations the reflex fails owing to vagus paralysis." This is approximately true for the salamander. But in the turtle stimulation of the large and small intestine, the urinary bladder and the cloaca in noncurarized animals causes chiefly an acceleration of the heart rate with a rise in blood pressure. In discussing the symptoms produced by distention of the gallbladder and biliary ducts in dogs, Schrager and Ivy [9] reported that changes in blood pressure and heart rate are caused, which, however, are not uniform. They expressed the belief that the reaction of the cardiovascular system to distention of the biliary passages is dependent on the functional state of the cardiovascular system at the time the distention occurs.

Buchbinder [10] has reported some interesting experiments in the frog in regard to the effects of incision of the gallbladder on cardiac activity. He observed that simple incision of the gallbladder in the frog causes a transient arrest of the heart, lasting from one to ten seconds, followed by a sinus bradycardia lasting from one to ten minutes. Occasionally, he observed dilatation and permanent arrest. These effects were attributed to a reflex vagus inhibition due to the acute change in pressure in the biliary tract incident to the incision of the gallbladder.

Because of the important clinical aspect of this experimental work, we decided to repeat it and to attempt a further analysis of the experiments. For example, in Buchbinder's experiment, the spillage of bile into the peritoneal cavity might play a rôle in the causation of the phenomenon he observed. He thought of this possibility, but discredited it by the statement that frog's bile in the amounts present in the gallbladder is innocuous for the heart. Therefore, in our experiments we have given particular attention to the spillage of bile and intestinal contents.

EXPERIMENTAL RESULTS

Since our experiments were performed on 130 frogs and 10 dogs, it is impracticable to give the protocols or details of the experiments. We shall merely summarize the results of the different groups of experiments.

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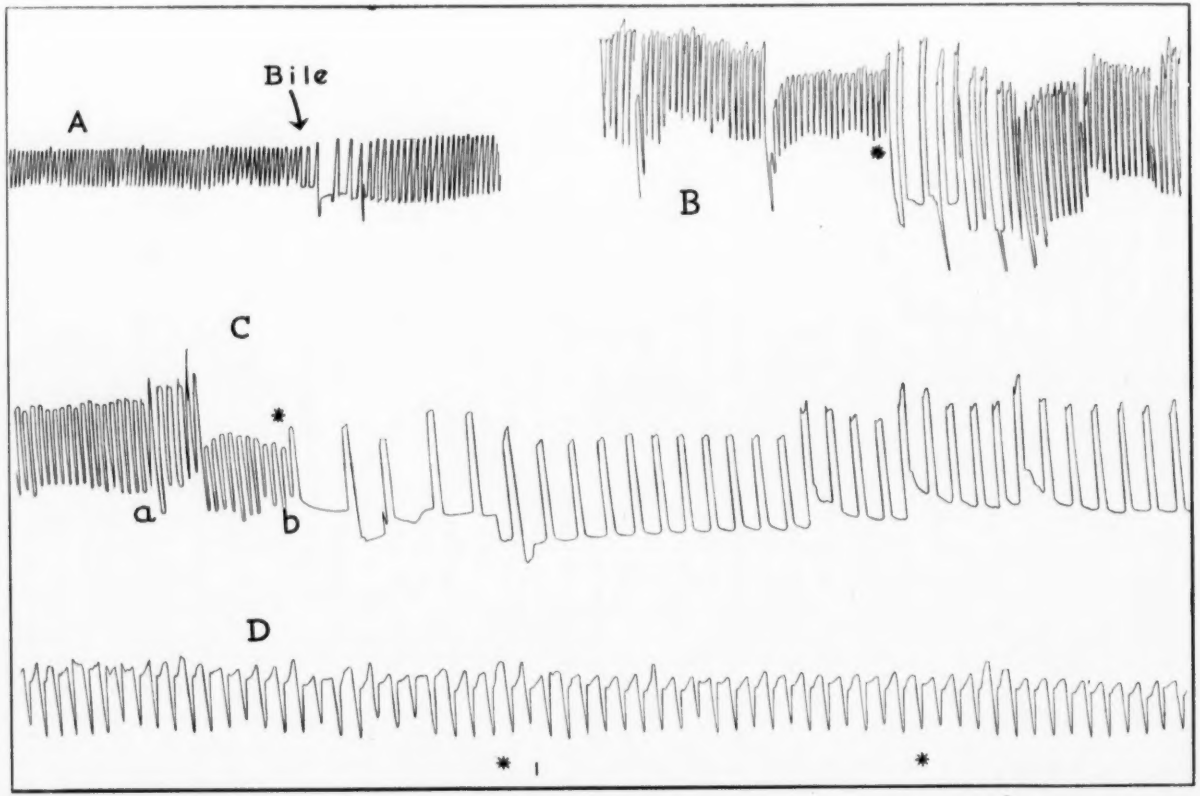
8. Carlson, A. J., and Luckhardt, A. B.: Am. J. Physiol. **55**:31, 1921.

9. Schrager, V. L., and Ivy, A. C.: Surg., Gynec. & Obst. **47**:1928.

10. Buchbinder, W. C.: Proc. Soc. Exper. Biol. & Med. **27**:542, 1930; Experimental Obstructive Jaundice, Arch. Int. Med. **42**:743 (Nov.) 1928.

The results in the frogs were uniform under certain conditions. It was found that in order to obtain viscerocardiac reflexes in the frog, it must not be anesthetized and must be fully recovered from the shock incident to decerebration, the reflexes being obtained best in intact frogs, and then only in about one half of the frogs used. All frogs were anesthetized during the operative procedures of decerebration, spinal pithing, demedullation and exposure of viscera for stimulation, but in every instance sufficient time was allowed for the effect of shock and anesthesia to pass away. The observations of Carlson and Luckhardt [8] on the cardio-inhibitory effect of traction, pinching the abdominal and pelvic viscera in the frog, were confirmed. No effect was observed unless the medullocardiac reflex mechanisms remained intact.

Ninety-nine of the experiments on frogs were directed to a study of stimulation of the gallbladder and spillage of bile. It was found that incision of the gallbladder in the decerebrate or intact frog caused cardiac inhibition uniformly and sometimes permanent (one-half hour) cardiac arrest, which confirmed the observations of Buchbinder. If pressure was exerted on the gallbladder or biliary tract area or if they were pinched, cardiac inhibition did not result. However, if this procedure was carried out so that traction was exerted on the liver or portal elements, cardiac inhibition would sometimes result. Also, if the bile was withdrawn by syringe and needle or prevented from spilling into or excluded from the peritoneal cavity, no cardiac inhibition would result. Further, if the cystic duct was carefully tied and the gallbladder with its bile carefully removed, inhibition would not occur. When the excised gallbladder containing bile was incised so that the bile spilled into the upper peritoneal cavity, cardiac inhibition occurred. Or, if bile was withdrawn from the gallbladder into a syringe and then slowly ejected from the syringe on to the abdominal viscera, the heart was inhibited. The inhibition of the heart following the contact of from 0.1 to 0.3 cc. of bile with the peritoneum was not due to the fact that the bile spread upward and bathed the heart, since this can easily be prevented in most frogs. The direct application of frog's bile (from 0.1 to 0.3 cc.) to the heart or to the pelvic peritoneum or the injection of bile into the dorsal lymph sac in the recovered decerebrate frog causes no alteration in the cardiac rhythm. It was noted that the intensity of the effect depended to a certain extent on the character of the bile. The darker, more concentrated bile had a more marked effect. There was also a quantitative relationship between the amount of bile released into the peritoneal cavity and the type and duration of the effect. It was noted that small quantities of less concentrated bile produced an initial acceleration of the heart rate, and in two instances this was the only effect. A second application of bile to the same area of the



Tracing *A* shows the effect on the heart of a frog of 0.1 cc. of bile from another frog injected into the upper peritoneal cavity. Tracing *B* shows the effect on the heart of an incision of the gallbladder, without the bile coming into contact with the heart. Tracing *C* shows: *a*, no appreciable effect on withdrawal with a syringe of the bile from the gallbladder, and *b*, the effect of introducing the withdrawn bile into the upper peritoneal cavity in the region of the gallbladder. Tracing *D* shows no effect produced by distention of the gallbladder and biliary passages.

peritoneal cavity of the recovered decerebrate frog caused no further change in the cardiac rhythm in the presence of the persisting bradycardia. In most instances the presence of an intact medullocardiac reflex mechanism was necessary for the effect, but inhibition occurred in three of fifteen experiments. The cardiac inhibition caused by spillage of bile into the peritoneal cavity is more marked and uniform than that caused by tapping, pinching or stretching the abdominal viscera, and makes a striking classroom demonstration. In view of these observations, we attribute the effects of incision of the gallbladder on the heart rate in the frog to spillage of bile into the peritoneal cavity. The presence of bile in the peritoneal cavity chemically instead of mechanically excites a reflex mechanism that results in cardiac inhibition, bradycardia or arrest.

In six frogs the gallbladder was cannulated, and the gallbladder and biliary passages were distended. In four no change in the heart was noted; in one the rate was slightly decreased, and in one the rate was definitely accelerated.

The effect of dog's gallbladder bile and hepatic bile in the upper peritoneal cavity of unanesthetized dogs on the cardiac rhythm and the blood pressure was studied in five animals. Blood pressure tracings were made on unanesthetized dogs with previously exteriorized carotid arteries simultaneously with the introduction of the bile (from 25 to 50 cc.) by means of a hollow needle and syringe into the upper peritoneal cavity. A slight rise in blood pressure and an acceleration in cardiac and respiratory rates were the only effects noted in these experiments.

In five other dogs the effect of distention of the extrahepatic ducts was studied. The cystic duct was cannulated after ligation of the common duct, and the carotid artery on one side was exteriorized. The cannulated duct was connected to a rubber tube that was brought to the outside through the abdominal incision. The next day, blood pressure tracings were made of the unanesthetized dogs, and the effect of distending the ducts with air was noted. In one dog the initial distention of the ducts caused a marked slowing of the respiratory and cardiac rates. In the other dogs no definite uniform effect was obtained.

COMMENT

The results of the experiments on the frog show decisively that the chemical and mechanical stimulation of most abdominal viscera in the frog may reflexly excite the cardio-inhibitory mechanism. We were somewhat surprised and disappointed to find that mechanical stimulation and even distention of the frog's gallbladder and biliary passages had no effect on the cardiac rhythm analogous to that sometimes observed

when a similar stimulus was applied to the stomach or the intestines. It is worthy of note that traction on the liver or portal elements sometimes had an inhibitory effect; however, because of the close anatomic relationship of the liver to the heart this is difficult to interpret, although it was not observed to occur in demedullated frogs.

The interesting observation of Buchbinder [10] on cardiac inhibition following incision of the gallbladder is due, as our results show, to local chemical irritation by the bile of nerve endings in the peritoneum or surrounding organs which reflexly excites the cardio-inhibitory mechanism. The failure to obtain cardiac inhibition in the dog when bile was injected into the peritoneal cavity (we observed acceleration) shows that the viscerocardiac reflex mechanisms are different from those of the frog; Carlson and Luckhardt [8] found this to be the case in the turtle.

The results on distention of the biliary passages of the dog confirm but are not so striking as those of Schrager and Ivy,[9] who observed extrasystoles in one dog. The effect on the heart and blood pressure is not uniform. Either inhibition or acceleration of the heart may result. The best explanation of this variation is that suggested by Schrager and Ivy, namely, "that the reaction of the cardio-vascular system to distention of the biliary passages is dependent on the functional condition of the cardio-vascular system at the time the distention occurs." The effect of distention of the biliary passages in the frog was even less effective than in the dog. In the cat a rise in blood pressure (pain?) occurs on distention of the common bile duct without a decided change in the heart rate.[11]

The experimental evidence does not indicate positively the existence of a direct reflex connection between the biliary passages and the cardiac activity, since a definite disturbance of the heart on stimulation of the biliary tract is the exception rather than the rule. It must be kept in mind, however, that in the experiments performed on dogs and frogs up to the present time, only normal mechanisms have been excited presumably. Whereas the patients considered in this discussion have a pathologic condition of the biliary tract and, in some instances at least, an abnormal heart and possibly in all cases a functionally "abnormal" or "irritable" heart. Experiments are yet to be done on animals with an abnormal condition of the biliary tract and heart. Also, the cardiac disturbances associated with disease of the biliary tract or visceral disease in general may not be due primarily or directly to a viscerocardiac mechanism, but secondarily to the cardiocirculatory changes known to be caused by nausea, vomiting, pain and respiratory disturbances. Of

11. Sherrington, C. S.: Integrative Action of the Nervous System, New Haven, Yale University Press, 1920, p. 11.

course, man may possess a direct or more sensitive viscerocardiac mechanism; this is not likely, since all patients with pathologic conditions of the biliary tract or other viscera do not manifest cardiac abnormalities.

CONCLUSIONS

The observations of Carlson and Luckhardt [8] on the cardio-inhibitory effect of mechanical stimulation of the abdominal and pelvic viscera and on the reflex mechanism concerned in this effect have been confirmed.

The gallbladder and biliary passages may be pinched and stretched without causing a change in the cardiac rhythm of frogs that show cardiac inhibition on mechanical stimulation of other abdominal viscera. The distention of the biliary passages in the frog usually causes no change in the heart, although either slight slowing or acceleration in rate occasionally may be observed.

The incision of the gallbladder of the frog so that bile is spilled into the upper abdominal cavity without coming in contact with the heart causes cardiac inhibition, which is due to a reflex inhibition of the heart caused by the irritant action of bile on the peritoneum and not to the toxic action of bile on the heart. Bile introduced into the upper portion of the peritoneal cavity of the dog causes acceleration of the heart instead of inhibition.

The observations of Schrager and Ivy on the effect of distention of the biliary passages in the "normal" dog have been confirmed essentially, a slowing of cardiac rate being observed in one of five dogs and no definite or uniform effect being observed in the others.

The bearing of these results on the alleged association of disease of the biliary tract with cardiac abnormalities in man is briefly discussed.

EXPERIMENTAL STUDIES ON THE EFFECT OF SECTION OF THE VAGUS NERVE ON GASTRIC SECRETION *

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AND
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Much interest has been manifested in recent years concerning the effect of section of the vagus nerve on the functions of the stomach. This procedure has been performed experimentally in animals and is now frequently recommended in gastric surgery in the treatment for peptic ulcer. It is commonly reported that there is a decrease in the gastric acidity after section of this nerve following subtotal gastrectomy. Considerable literature on this subject has accumulated in recent years. It may be said in general that most observers have noted a decrease in the gastric secretion following vagus section. It, however, appears from the literature that in the larger proportion of these experiments the observations have been followed only for a short period of time. What the results might have been after prolonged observations of these animals has up to the present not been clearly established.

McCrea [1] investigated this subject most intensively from the experimental standpoint. He concluded that the commonly accepted view that the left vagus is distributed to the anterior surface of the stomach and the right to the posterior is incorrect, as each supplies fibers to both surfaces. The vagus nerve possesses both accelerator and inhibitor fibers, but is largely accelerator in its function. He pointed out that resection of both vagi in the neck proves fatal, while section of one vagus or one splanchnic nerve is without effect. McCrea further asserted that vagal section results in dilatation, diminished tonus, decreased peristalsis and delayed emptying of the stomach. Splanchnic section, on the other hand, has the reverse effect. The section of all nerves gives results similar but somewhat less marked than vagal section alone. According to this observer, these results are not permanent, but following a period of time the tonus is restored, and peristalsis becomes normal. He considered it doubtful whether any actual permanent influence, either on secretion or on acidity, is produced.

* Submitted for publication, May 4, 1931.

* From the Gastro-Enterological Clinic of the Department of Medicine, University of Maryland.

1. McCrea, E. D'A.: Brit. J. Surg. **13**:621 (April) 1926.

Psychic and reflex secretion disappears on vagal section, and although the secretory curve is altered, acid juice still continues to be secreted.

Attention may be directed to other experimental work on the resection of the vagi recorded by various observers. Lorenzi [2] reported his results of resection of these nerves, either in the neck or below the diaphragm in rabbits. He noted that hemorrhages were frequently produced in the mucous membrane of the stomach, and that in some instances hemorrhagic erosions developed. Saitta [3] was able to produce multiple ulcers in certain rabbits following bilateral vagotomy after the administration of a 3 per cent solution of muriatic acid. Yzeran [4] severed both vagi below the diaphragm in twenty rabbits and succeeded in producing chronic ulcers in the pyloric region of the stomach in ten. In 1906, Cannon [5] observed, as a result of severing the vagi bilaterally below the origin of the recurrent laryngeal nerve, a disturbance of the motor function of the stomach, at first, but recovery occurred within a few days.

Ophuls [6] resected both vagi below the diaphragm and produced gastric ulceration in six of eighteen rabbits in twenty-four days. He observed but slight changes in the gastric secretion. In Auer's [7] experiments in which both nerves were resected in the neck in rabbits, death quickly ensued. By severing both nerves below the diaphragm, gastric ulcers were produced in some instances. Portis and Portis [8] produced a true achylia by means of a subtotal gastrectomy in dogs. Whether this was due, however, to removal of a nerve center located at the incisura is considered doubtful. Hughson [9] observed a diminution in the normal emptying time of the stomach in dogs following resection of the vagus nerves. Klein [10] reported his results in eight cases of duodenal ulceration associated with marked hyperacidity in which partial gastrectomy was performed. In but one quarter of these cases could an anacid state be obtained. In eight cases, however, in which in addition section of the left vagus was performed, anacidity occurred in all. Hartzell [11] observed that following section of the vagus nerve in

2. Lorenzi: Rassegna de sc. med. **8**:313, 1893.
3. Saitta: Gaz. d. osp. **21**:599, 1900.
4. Yzeran: Ztschr. f. klin. Med. **43**:181, 1901.
5. Cannon: Am. J. Physiol. **17**:429, 1906-1907.
6. Ophuls: J. Exper. Med. **8**:181, 1906.
7. Auer: Am. J. Physiol. **25**:334, 1909-1910.
8. Portis, B., and Portis, S. A.: Effect of Subtotal Gastrectomy on Gastric Secretion: Experimental Study by Aid of Pavlov Pouch in Dogs, J. A. M. A. **86**:836 (March 20) 1926.
9. Hughson, W.: Effect of Vagus Neurotomy on Pyloric Sphincter: Experimental Study, J. A. M. A. **88**:1072 (April 2) 1927.
10. Klein, E.: Ann. Surg. **90**:65, 1929.
11. Hartzell, J. B.: Am. J. Physiol. **91**:161, 1929.

the neck, changes in the gastric secretion occurred in the form of a reduction of both free hydrochloric acid and total acidity. In those animals, however, in which the branches of the vagus were sectioned in the abdomen a normal secretion of free hydrochloric acid was occasionally noted.

Burkle-de-la Camp [12] was able to bring about, by means of subcutaneous injections of histamine, a flow of gastric juice of such high acidity as to produce peptic ulcerations in rats. This occurred even following division of both vagi. Pieri and Tanferna [13] performed in six of nine persons with recurring ulcers, supradiaphragmatic resection of the left vagus, while in the other three bilateral resection was made under the diaphragm. He observed a lowering of the hydrochloric acid and of the pepsin. Later, however, both the hydrochloric acid and pepsin content rose steadily and in some instances regained and even exceeded the previous figures. Thompson [14] likewise found that bilateral vagotomy lowered the gastric secretion in the pylorectomized stomach of the dog. He also pointed out, on the other hand, the fact that following this operation meals of ordinary size may contain sufficient protein to neutralize all of the hydrochloric acid that the fundus is capable of secreting.

Winkelstein [15] called attention to the effect of vagus section in establishing a reduction in the gastric acidity following partial gastrectomy for ulcer. Berg [16] likewise reported his results following the division of the left pneumogastric nerve, which he performs regularly in all patients who have high acidities prior to subtotal gastrectomy in the treatment for ulcer. He found that these patients become anacid in from two weeks to several months following section of the left vagus nerve.

EXPERIMENTAL WORK

As considerable doubt still remains as to the permanent effect of vagal section on gastric secretion, it was considered of sufficient importance to investigate this problem further. This work was greatly facilitated by the operative aid given us by Dr. Alfred Ullman and Dr. Ferdinand A. Ries.

Twenty-two dogs were utilized in these experiments. Healthy adult dogs of medium size were selected for the purpose. Psychic influences were eliminated as far as possible by allowing the dogs to become familiar with their laboratory environment for some time. Repeated

12. Bürkle-de-la Camp: Deutsche Ztschr. f. Chir. **220**:31, 1929.
13. Pieri, G., and Tanferna, U.: Riforma med. **46**:323, 1930.
14. Thompson: Proc. Staff Meet., Mayo Clin. **5**:88, 1930.
15. Winkelstein, A.: Am. J. Surg. **7**:494, 1929.
16. Berg, A. A.: Ann. Surg. **92**:340, 1930.

analyses were made before operation to accustom the animals to the use of the tube. The following methods of obtaining the gastric contents were utilized:

1. Fifty cubic centimeters of 7 per cent solution of alcohol was introduced into the fasting stomach through a tube, and the contents were extracted in forty minutes.

2. One and a half milligrams of histamine (ergamine acid phosphate) was injected subcutaneously during the fasting state, and the

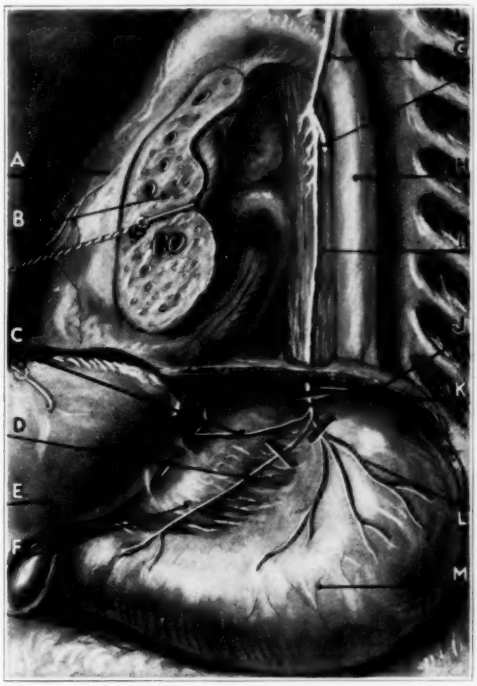

Fig. 1.—Drawing illustrating the distribution of the main gastric branches of the left vagus nerve. The nerve was severed at the three points indicated by the black cross-line. *A* indicates the heart; *B*, the cut surface of the left lung; *C*, the hepatic branch; *D*, the anterior nerve; *E*, the lesser curvature of the liver; *F*, the omentum minus; *G*, the left vagus nerve; *H*, the aortae, thoracalis; *I*, the gastric secretion in a dog in which the vagus nerve was severed below the diaphragm; *L*, anterior gastric branches, and *M*, the stomach.

contents of the stomach were extracted in thirty minutes. Weekly or biweekly extractions were performed regularly on each animal.

These secretions were examined for free hydrochloric acid and total acidity according to the usual method. The utilization of test meals

containing food as is ordinarily practiced for obtaining gastric contents has been found unsatisfactory in animals, whereas the alcohol and histamine stimulation has proved to be far more trustworthy.

After the normal findings were definitely established, the vagus nerve was severed, as will be later described. Frequent gastric analyses were again performed, and the results compared with those obtained from the normal animal. It was deemed best in order that these comparisons could be properly evaluated that an average be obtained. This was accomplished by averaging the results of numerous test meals obtained before and following operation.

In nine dogs, following the alcohol test meal, the normal average of hydrochloric acid was 22 and the total acidity 46. With the histamine

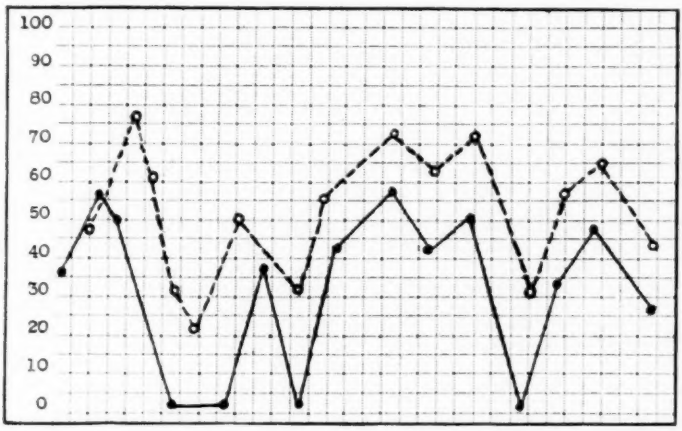

Fig. 2.—Chart illustrating the free hydrochloric acid and total acidity of the gastric secretion in a dog in which the vagus nerve was severed below the diaphragm. The irregularity of the acid curve, noted after fifteen weekly extractions, following histamine stimulation, is shown. Free acid is indicated by the solid line; total acid, by the broken line.

test, in ten dogs the normal average free hydrochloric acid was 65 and the total acidity 94.

It is important to note that the continued use of histamine as a stimulant to the gastric secretion was at no time followed by any ill effect, nor were there any lesions produced in the stomach as the result of this drug. The quantity of gastric contents obtained from animals after severance of the nerve differed in no way from that secured from the normal.

Following a thorough study of the normal gastric secretion in each dog, the vagus nerve and its branches were severed at various locations, under strict aseptic precautions. At each operation at least one half

an inch of the nerve was resected, and histologic studies were then made of this portion in order that there could be no doubt as to the removal of nerve tissue. Following operation, all of the dogs lost weight for a short period, which they gradually regained, with the exception of the group to be later described. During the entire period of the experiments, ranging from three to twelve months, the dogs were placed on the usual laboratory diet with the exception of the group just mentioned. Following the first two weeks most of the animals apparently enjoyed good health and suffered no ill effects as the result of the operation.

Roentgenologic studies were also made in order to determine whether delay in emptying of the stomach was produced by vagal section.

In the first group of ten dogs, the left vagus nerve was severed at a location just below the diaphragm. All of the animals showed a steady tendency to progressive loss of flesh with marked weakness, and unless placed under special dietetic regimen, died in a short time. In three of the ten dogs death followed quickly, and at autopsy acute peritonitis with free pus in the abdominal cavity was revealed. In three others, convulsive seizures developed before death. Four dogs were placed on a milk diet and increased in weight. They survived for a period of three months in an apparently healthy state; then they were killed. In these dogs, following histamine stimulation the gastric content showed an average free hydrochloric acid of 63 and a total acidity of 80, indicating that there was but a slight change produced in the secretions as compared with that noted before the operation.

In a second group of three dogs the anterior branch of the left vagus nerve was severed. These dogs lived nine months and were then killed. The average free hydrochloric acid following the alcohol test meal was 25; the total acid, 43. After stimulation with histamine, the average free hydrochloric acid was 36; the total acidity, 53. The results of the alcohol test meal compared closely with that observed in the normal, while those following histamine stimulation showed a marked decrease in the free hydrochloric acid and total acidity.

In a third group of two dogs the principal anterior branch of the left vagus nerve was severed; one dog died three weeks following the operation. The second dog, observed over a period of five and a half months, revealed an average free hydrochloric acid content of 16 and a total acidity of 42 following the alcohol test meal, and an average free hydrochloric acid of 55 and a total of 70 following the histamine stimulation. This experiment showed a slight decrease in the gastric acidity as compared with the normal.

In a fourth group of two dogs, the left vagus nerve was severed in the neck. These dogs were observed over a period of ten months. The free hydrochloric acid of the gastric secretion averaged 29 and the total acidity 46 with the alcohol test; following histamine stimulation, the free

hydrochloric acid averaged 39 and the total acidity, 55. It is evident that no marked changes were observed following the alcohol test meal, while the histamine test showed a marked diminution in both the free acid and the total acidity.

In a final group of two dogs, the right vagus nerve was severed in the neck, just below the recurrent laryngeal branch. The dogs were observed over a period of six and a half months. The average obtained following the alcohol test meal revealed a free hydrochloric acid of 18 and a total acidity of 38. The histamine stimulation showed an average free hydrochloric acid of 70 and total acidity of 81. These findings differ markedly from those obtained following the severance of the left vagus nerve in the neck, in that they compare more closely with the results obtained in the average normal.

It is of interest to state that the roentgenologic examination made in eight dogs following the vagal section revealed no delay in the emptying time of the stomach in the six hour study. At this period the stomach was found to be empty and the barium observed only in the terminal ileum and colon. In most instances the colon was only partially filled and a considerable amount of the opaque meal had been evacuated, indicating a hypermotility of the gastro-intestinal tract.

Complete autopsies were performed following death in all of the dogs in order to demonstrate that the proper nerve had been sectioned. The esophagus, stomach and duodenum were carefully investigated, and no lesions were detected in any instance. The mucous membrane of the stomach appeared normal, and there was no evidence of dilatation.

CONCLUSIONS

From these experiments the following conclusions may be drawn:

1. Section of the left vagus nerve immediately below the diaphragm produces but a negligible change in the gastric secretion as compared with the normal.

2. Following section of the anterior gastric branch of the left vagus nerve, the acidity may remain either normal or become markedly decreased.

3. Section of the principal anterior branch of the left vagus is followed by slight decrease in the gastric acidity.

4. After section of the left vagus in the neck, the secretion continues to be normal or there results a marked diminution in the acidity.

5. Following section of the right vagus nerve, the findings vary but slightly from the normal.

6. It is therefore evident that while at times changes in the gastric secretion occur owing to section of the vagus nerve, these are inconstant; there is likewise a general tendency for this secretion to return to normal when diminished as the result of this operation.

THE EFFECT OF BRONCHIAL ASTHMA ON THE CIRCULATION *

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The pathologic physiology of bronchial asthma is manifested by an edema of the mucous membranes and a spasm of the smooth muscle of the bronchi and bronchioles. The air passages become closed, and owing to this closure, there is subsequent difficulty in breathing, particularly in expiration. As a result of prolonged and frequent attacks of this type of dyspnea, the lungs become distended and emphysema supervenes. In the latter condition, the alveoli are distended, causing a flattening of the alveolar wall with consequent narrowing, tearing and even destruction of the capillaries, which results in diminution of alveolar circulation and increased pressure within the pulmonary arteries. Theoretically, this should result in increased work for the right ventricle.

This assumption seems to be borne out by Kahn,[1] who concluded from an electrocardiographic study of fifty cases of bronchial asthma that the majority of his patients demonstrated a state of hypertrophy of the right ventricle. This conclusion is based on the finding of right ventricular preponderance present in only one fifth of the entire series—a finding that he took to be identical with right ventricular hypertrophy. In a more recent report, Unger [2] went a step further and concluded from an electrocardiographic study of seventy-four cases of bronchial asthma that there was evidence of actual cardiac damage in his patients, as shown by the presence of mild conduction disturbances, right ventricular preponderance and a tendency toward such preponderance. The only other report on the subject is by Alexander, Luten and Kountz,[3] who, as a result of a painstaking and thorough study of

* Submitted for publication, May 14, 1931.

* From the Department of Internal Medicine and the Clinic of Applied Immunology, University of Pittsburgh.

* Read before the Society for the Study of Allergy and Allied Conditions, Atlantic City, May 2, 1931.

1. Kahn, M. H.: Electrocardiogram in Bronchial Asthma, Am. J. M. Sc. **173**:555 (April) 1927.

2. Unger, L.: Heart in Bronchial Asthma; Electrocardiographic Study of Seventy-Four Cases, J. Allergy **2**:17 (Nov.) 1930.

3. Alexander, H. L.; Luten, D., and Kountz, W. B.: Effect on the Heart of Long Standing Bronchial Asthma, J. A. M. A. **88**:882 (March 19) 1927.

fifty patients, found, unlike the observers quoted, that bronchial asthma has no deleterious effect on the heart.

Two questions therefore present themselves in this connection: Do repeated attacks of bronchial asthma produce cardiac damage? What is the state of the heart during an acute and severe paroxysm?

TABLE 1.—*The Heart*

Case	Age	Weight	Duration, Years	Family History	Associated Allergy	Skin Tests	Foci			Emphysema	Cardiac Etiology	Symptoms
							Sinusitis	Tonsils	Teeth			
1	42	180	20	Neg.	Negative	Pos.	Neg.	Pos.	Neg.	Present	None	None
2	14	78	5	Neg.	Negative	Pos.	Pos.	Pos.	Neg.	Absent	None	None
3	26	136	16	Pos.	Negative	Pos.	Pos.	Out	Neg.	Present	None	None
4	11	58	9	Pos.	Negative	Pos.	Pos.	Out	Neg.	Present	Scarlet fever	None
5	18	122	5	Neg.	Negative	Pos.	Neg.	Neg.	Pos.	Present	None	None
6	40	149	7	Neg.	Urticaria	Pos.	Pos.	Pos.	Neg.	Present	None	None
7	12	67	5	Neg.	Negative	Pos.	Neg.	Neg.	Neg.	Present	None	None
8	22	96	16	Neg.	Hay fever	Pos.	Pos.	Neg.	Pos.	Present	None	None
9	55	150	6	Pos.	Negative	Pos.	Neg.	Neg.	Neg.	Absent	Rheumatic fever	None
10	67	112	16	Neg.	Negative	Pos.	Pos.	Pos.	Pos.	Present	None	None
11	29	149	25	Pos.	Negative	Pos.	Pos.	Out	Out	Present	None	None
12	14	115	10	Neg.	Negative	Pos.	Neg.	Neg.	Neg.	Present	None	None
13	44	119	7	Neg.	Negative	Pos.	Pos.	Neg.	Neg.	Present	None	None
14	37	104	16	Pos.	Negative	Pos.	Neg.	Neg.	Neg.	Present	None	None
15	47	154	14	Neg.	Negative	Pos.	Neg.	Neg.	Neg.	Present	None	None
16	30	169	5	Neg.	Negative	Pos.	Pos.	Pos.	Neg.	Present	None	None
17	54	144	14	Pos.	Urticaria	Pos.	Pos.	Neg.	Neg.	Present	None	None
18	56	101	36	Pos.	Urticaria	Pos.	Pos.	Neg.	Neg.	Present	None	None
19	40	88	7	Pos.	Hay fever	Pos.	Pos.	Neg.	Neg.	Present	None	None
20	21	133	6	Neg.	Negative	Pos.	Neg.	Pos.	Neg.	Present	None	None
21	37	140	7	Neg.	Hay fever	Pos.	Neg.	Pos.	Neg.	Present	None	None
22	34	117	6	Neg.	Hay fever	Pos.	Neg.	Neg.	Neg.	Present	None	None
23	26	134	14	Pos.	Negative	Pos.	Neg.	Pos.	Neg.	Present	None	None
24	32	150	11	Pos.	Negative	Pos.	Neg.	Neg.	Pos.	Present	None	None
25	32	170	8	Pos.	Hay fever urticaria	Pos.	Neg.	Pos.	Neg.	Present	Rheumatism	None
26	30	180	11	Pos.	Negative	Pos.	Neg.	Out	Neg.	Present	Rheumatism	None
27	31	202	5	Neg.	Negative	Pos.	Neg.	Neg.	Neg.	Present	Rheumatism	None
28	21	85	12	Pos.	Eczema	Pos.	Neg.	Neg.	Neg.	Present	Rheumatism	None
29	57	137	5	Neg.	Negative	Pos.	Neg.	Pos.	Neg.	Present	Rheumatism	None
30	25	115	20	Pos.	Hay fever	Pos.	Pos.	Neg.	Neg.	Present	Rheumatism	None
31	38	208	8	Neg.	Urticaria	Pos.	Pos.	Pos.	Neg.	Present	Rheumatism	None
32	38	165	27	Neg.	Rhinitis	Pos.	Pos.	Pos.	Pos.	Present	Rheumatism	None
33	6	40	5	Pos.	Negative	Pos.	Neg.	Out	Neg.	Present	Rheumatism	None
34	11	78	10	Pos.	Negative	Pos.	Neg.	Out	Neg.	Present	Rheumatism	None
35	57	137	15	Pos.	Negative	Pos.	Pos.	Neg.	Neg.	Present	Rheumatism	None
36	43	130	20	Neg.	Negative	Pos.	Neg.	Out	Neg.	Present	Rheumatism	None
37	46	145	7	Neg.	Negative	Pos.	Neg.	Out	Pos.	Present	Rheumatism	None
38	42	132	15	Pos.	Negative	Pos.	Neg.	Neg.	Neg.	Present	Rheumatism	None
39	67	126	20	Pos.	Negative	Pos.	Neg.	Neg.	Neg.	Present	Rheumatism	None
40	43	187	9	Neg.	Negative	Pos.	Neg.	Neg.	Neg.	Present	Rheumatism	None
41	29	129	21	Pos.	Hay fever	Pos.	Neg.	Out	Pos.	Present	Rheumatism	None
42	23	124	6	Pos.	Negative	Pos.	Neg.	Out	Neg.	Absent	Rheumatism	None
43	23	110	5	Pos.	Negative	Pos.	Pos.	Neg.	Neg.	Absent	Rheumatism	None
44	51	181	42	Pos.	Negative	Pos.	Neg.	Pos.	Pos.	Present	Rheumatism	None
45	25	115	22	Pos.	Negative	Pos.	Pos.	Neg.	Neg.	Absent	Rheumatism	None
46	48	162	30	Pos.	Negative	Pos.	Pos.	Out	Neg.	Present	Rheumatism	None
47	8	45	7	Pos.	Negative	Pos.	Neg.	Pos.	Neg.	Absent	None	None
48	40	168	6	Pos.	Negative	Pos.	Pos.	Neg.	Neg.	Present	None	None
49	43	136	40	Pos.	Hay fever	Pos.	Pos.	Out	Neg.	Present	None	None
50	43	158	5	Pos.	Negative	Pos.	Pos.	Pos.	Pos.	Absent	None	None

* The abbreviations occurring in table 1 are explained thus: M.R. stands for the transverse diameter of the
L.D. the long diameter; S.A. equals sinus arrhythmia; L.V.P. equals left ventricle preponderance, and R.V.P.

EFFECT OF REPEATED ATTACKS OF BRONCHIAL ASTHMA ON THE HEART

For the purpose of this study a series of fifty consecutive cases of bronchial asthma was used. This material was obtained both from the clinic and from private practice. Only the following patients were

in Bronchial Asthma *

	Blood Pressure				Ventricular Pressure		X-Ray (6 ft.)				Vital	Electrocardiograms	
Rate	Systolic	Diastolic	Murmur	Effort Test	Between Attacks	During Attacks	M.R.	M.L.	Tr.	L.D.	Capacity	Between Attacks	During Attacks
84	130	90	Funct.	Good	7.0	...	5.0	10.6	15.6	15.5	71	S.A., L.V.P.	.....
90	120	70	None	Good	6.5	...	3.0	6.2	9.2	11.0	101	L.V.P.	.....
84	118	80	None	Good	7.5	...	4.4	6.3	10.7	11.7	70	S.A., L.V.P.	L.V.P. latent block
90	100	65	None	Good	8.0	9.0	2.7	5.5	8.2	9.0	56	S.A., R.V.P.	.....
80	90	60	None	Good	6.5	...	3.6	5.7	9.5	9.5	42	Normal	.....
80	100	70	None	Good	7.0	...	4.1	9.0	13.1	14.5	76	S.A.	.....
82	95	56	None	Good	6.5	10.5	2.9	6.5	9.4	10.0	89	R.V.P.	.....
86	110	85	None	Slight limit.	6.0	10.5	3.8	6.1	9.9	10.6	92	L.V.P.	P.B. of right V. source
88	140	90	None	Good	5.5	...	3.0	9.8	12.8	13.1	90	L.V.P.	.....
87	100	60	None	Slight limit.	6.0	...	3.5	8.2	11.7	12.3	70	S.A.	.....
78	160	70	None	Good	8.0	9.0	4.1	7.5	11.6	12.5	49	Normal	.....
100	110	80	None	Good	7.5	...	3.3	6.5	9.8	11.2	55	S.A., L.V.P.	.....
77	100	65	None	Limit.	5.5	8.0	3.6	8.2	11.8	12.7	74	S.A.	.....
96	100	80	None	Good	6.0	8.5	3.7	7.1	10.8	12.5	80	S.A.	.....
84	135	80	None	Good	6.5	...	4.2	8.2	12.5	14.0	92	S.A., L.V.P.	.....
84	135	75	None	Good	7.0	9.0	4.5	7.6	12.8	12.1	62	Normal	Normal
90	164	100	None	Good	7.5	...			Normal		..	Normal	.....
88	120	60	None	Good	8.5	...			Normal		..	Normal	.....
90	115	85	None	Good	7.0	...			Normal		..	Normal	.....
80	100	70	None	Good	5.3	...	4.0	7.5	11.5	12.5	52	S.A., L.V.P.	.....
80	120	69	None	Good	6.4	...			Normal		68	Normal	Normal
80	100	62	None	Good	...	...	3.5	8.5	12.0	13.0	73	Normal	.....
84	110	68	None	Good	...	...	...	...	....	....	101	Normal	.....
80	115	70	None	Good	5.5	9.5	4.6	7.0	11.6	12.5	59	Normal	Normal
94	154	80	Mitral	Slight limit.	6.0	10.4	4.0	8.0	12.0	13.0	65	R.V.P.	.....
54	110	65	None	Good	7.0	...	4.5	6.5	11.0	11.5	78	S.A., L.V.P. and bradycardia	.....
82	150	80	None	Good	5.5	...	...	...	....	....	78	S.A.	.....
86	105	65	None	Good	5.0	...			Normal		68	L.V.P.	.....
90	148	83	None	Good	...	...			Normal		72	S.A.	.....
84	110	50	Funct.	Good	6.5	...	3.7	7.3	11.0	12.5	54	Normal	Normal
94	170	80	Funct.	Good	7.0	...	5.5	9.0	14.5	14.5	56	Normal	.....
80	140	63	None	Good	7.5	...	4.0	8.0	12.0	12.5	79	S.A.	.....
84	70	40	None	Good	6.0	...	...	...	....	....	89	Normal	Normal
85	100	52	None	Slight limit.	6.5	...	...	...	....	....	86	Normal	Normal
80	108	70	None	Good	6.5	...	4.0	6.5	10.5	12.0	73	S.A.	.....
88	140	74	None	Good	7.0	8.5	3.5	7.0	10.5	13.0	..	S.A.	.....
90	140	75	None	Good	8.0	...	...	...	....	....	64	Normal	.....
96	138	68	None	Good	6.5	...			Normal		65	Normal	.....
80	130	70	None	Good	5.4	...			Normal		73	S.A.	.....
82	160	72	None	Good	5.8	...			Normal		67	P.B.	.....
78	100	50	None	Good	5.9	...	4.5	6.0	10.5	11.0	..	S.A.	.....
76	120	60	None	Good	6.5	...	4.0	7.0	11.0	11.5	..	Normal	.....
84	105	80	None	Good	6.4	...	3.5	7.5	11.0	12.0	53	S.A.	.....
76	120	70	None	Good	5.8	...	5.0	8.1	13.1	13.5	49	S.A.	.....
82	110	50	None	Good	6.2	...	3.5	7.0	10.5	12.0	76	S.A.	.....
88	145	80	Mitral	Good	6.0	...	4.0	6.0	10.0	11.0	..	R.V.P.	.....
92	83	56	None	Good	5.0	...	...	...	....	....	..	Normal	.....
82	130	64	None	Good	7.0	...	4.1	7.8	11.9	12.6	..	Normal	.....
80	120	65	None	Good	5.0	...	4.5	8.2	12.7	13.5	..	Normal	.....
87	128	64	None	Good	7.5	...	4.0	8.5	12.5	13.0	..	Normal	.....

heart to the right of the midline, and M.L. that to the left of the midline; Tr. is the total transverse diameter, and right ventricle preponderance; P.B. equals premature beats, and V. equals ventricular.

included: those who gave an unmistakable history of paroxysmal seizures and asthmatic symptoms; those who gave a personal history of some additional allergic manifestation, such as hay fever or hives, and a positive familial history, and those who gave positive skin tests to either the inhalant or ingestant group of proteins. No patient was included whose history of attacks did not cover a period of at least five years. The distribution of the patients in this group with regard to the duration of their illness may be seen in table 2 and fig. 1. There were twenty in whom the duration of the condition was between five and ten years, and nine who had been ill for from ten to fifteen years.

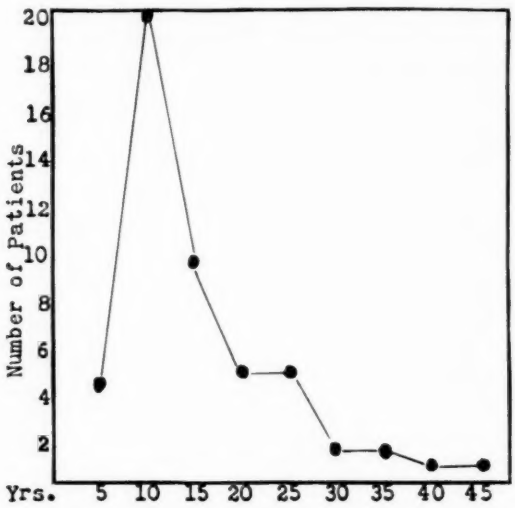

Fig. 1.—Graph of the number of patients and duration of illness.

Table 2 and fig. 2 show the distribution of patients with reference to age. Thirty-four of the fifty patients were from 20 to 50 years of age. Of the entire group, sixteen presented no evidence of foci of infection in the tonsils, teeth or sinuses. Twenty-three had infected sinuses; fourteen showed diseased tonsils, and nine presented some evidence of apical infection in the teeth (table 3).

These patients were subjected to a thorough clinical and laboratory cardiac investigation. The clinical survey comprises a cardiac history and physical examination. The laboratory data consist of vital capacity and venous pressure determination, electrocardiographic tracings and complete cardiac measurements obtained from roentgenograms of the chest taken at a distance of 6 feet (183 cm.). These studies were

carried on during the asthma-free period, and show the following results: Two of the patients had rheumatic mitral disease, a condition that was independent of, and anteceded, their asthma. Two more

TABLE 2.—*Findings in Bronchial Asthma*

Age of Patients			Duration		
Years	Number	Per Cent	Years	Number	Per Cent
5–10	2	4	5	5	10
10–20	6	12	5–10	20	40
20–30	12	24	10–15	9	18
30–40	11	22	15–20	5	10
40–50	11	22	20–25	5	10
50–60	6	12	25–30	2	4
60–70	2	4	30–35	2	4
			35–40	1	2
			40–45	1	2

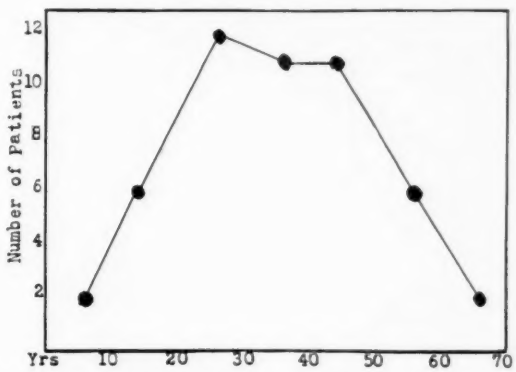

Fig. 2.—Graph of the distribution of the disease according to the age of the patients.

presented apical systolic murmurs which were definitely functional. Four patients showed some restriction in their response to effort, both as regards increasing fatigue and abnormal reaction of pulse and blood pressure following such exercise as walking up one flight of steps. The rest of the cardiac examination, however, did not indicate the presence of cardiac damage. As seen in table 1, hypotension was almost the rule in the entire group. What its underlying mechanism was does not seem entirely clear. It is certain, however, that it was not due to myocardial damage, but that it might be due to possible involvement of the autonomic nervous system. The majority of the patients showed a reduction in vital capacity that ranged from 49 to 100 per cent of the normal, with an average reduction of 61 per cent for the group

(table 3 and fig. 3). The calculations are made according to the tables of West and Meyers.[4] The diminution in vital capacity in all likelihood was due to the presence of emphysema, for in only seven of the

TABLE 3.—*Findings in Bronchial Asthma*

Vital Capacity			Foci of Infection		
Reading, per Cent	Number	Per Cent	Source	Number	Per Cent
40- 50	3	7.5	Tonsils	14	28
50- 60	7	18	Teeth	9	18
60- 70	7	18	Sinuses	23	46
70- 80	13	34	None	16	32
80- 90	4	10			
90-100	3	7.5			
100-110	2	5			

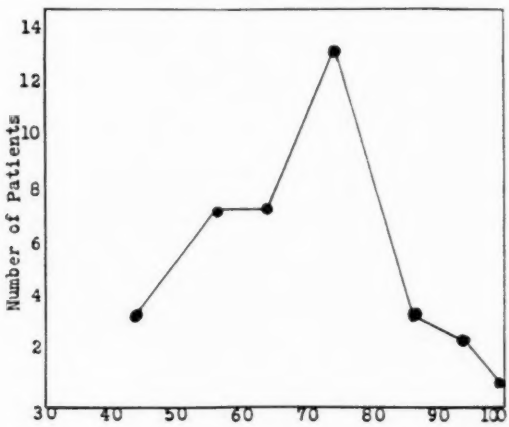

Fig. 3.—Graph of the vital capacity of patients with bronchial asthma.

fifty patients was emphysema entirely absent. The venous pressure as determined by the indirect method during the asthma-free period was well within normal, ranging from 5.5 cm. to 8 cm. of water. It showed, however, a tendency to rise during the acute paroxysm (table 1).

In the interpretation of electrocardiograms, a tracing is considered normal if it shows no evidence of arrhythmia; if the P-R (auriculoventricular) interval does not exceed 0.2 second; if there is no preponderance of the right or left ventricle, and if there is no abnormality of the various representatives, particularly the T wave, an abnormality that so frequently denotes myocardial or coronary disease. It

4. Meyers, J. A.: Vital Capacity of the Lungs, Baltimore, Williams & Wilkins Company, 1925.

is interesting to note that of the entire series, 42 per cent showed mild grades of sinus arrhythmia (tables 1 and 4, and fig. 4). The incidence of this finding was apparently independent of the age of the patient.

TABLE 4.—*Electrocardiogram in Bronchial Asthma*

Duration, Years	Electrocardiogram					
	Normal	S.A.	L.V.P.	R.V.P.	Cond.	Myoc.
5-10	12	8	5	2	P.B. 1	0
10-20	5	7	5	1	0	0
20-30	1	5	0	1	0	0
30-40	1	1	0	0	0	0
40-50	2	0	0	0	0	0
Total	21	21	10	4	1	0

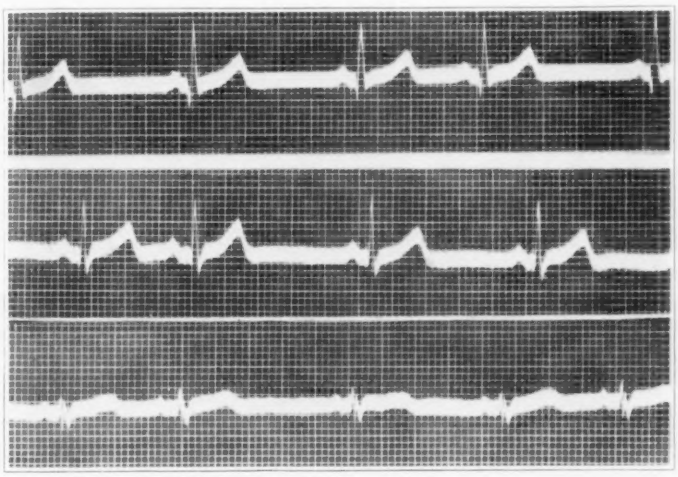

Fig. 4 (case 13).—Marked sinus arrhythmia; vagus effect; three leads.

Ten patients, or 20 per cent, showed left ventricular preponderance, and four patients, or 8 per cent, showed right ventricular preponderance. However, of these four patients, two had mitral disease, and right ventricular preponderance is not an uncommon finding in this condition. Occasional premature beats of ventricular origin were found in one instance. The rest of the series, twenty-one patients, or 42 per cent, presented entirely normal tracings. It should be noted that this percentage would be more than doubled if sinus arrhythmia and ventricular preponderance were not considered abnormal. Sinus arrhythmia in these cases was due to the vagotonia with which bronchial asthma is so frequently associated. This vagus effect is shown particularly in case 26 which presents the electrocardiographic picture of

sinus arrhythmia, left ventricular preponderance and a marked bradycardia, with a rate of 40 (fig. 5). The clinical significance of ventricular preponderance is apparently not very great. As an isolated finding, it is not infrequently seen in normal persons, and presents itself as a result of numerous factors other than cardiac impairment. As a matter of fact, while it was thought originally that preponderance of a ventricle is synonymous with increase in ventricular muscle mass, and that preponderance is a fairly reliable means of estimating the relative weight of the ventricles, this view has undergone some modification. It is shown that the position of the heart in the chest is a determining factor, and more recently Fahr,[5] and Herman and

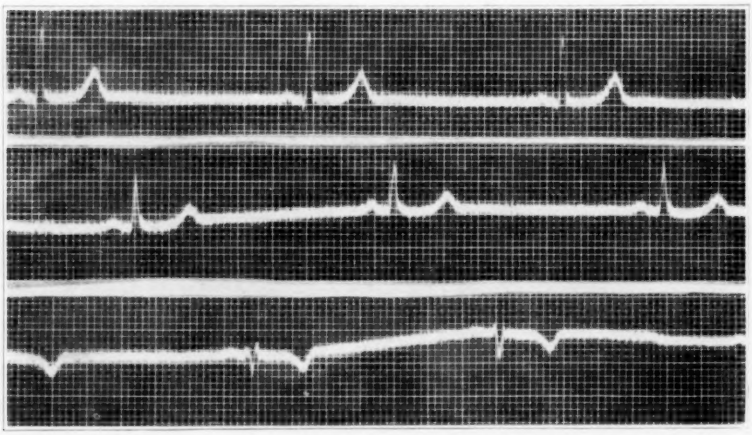

Fig. 5 (case 26).—Sinus arrhythmia; bradycardia; left ventricular preponderance.

Wilson[6] showed that the picture of preponderance may be affected by the propagation of the impulses through, and the anatomic distribution of, the conduction system; that what is now considered right preponderance may be left preponderance, and vice versa. To substantiate this view, Barker and his co-workers[7] presented fairly definite evidence by showing that what is now interpreted as premature beats of left ventricular origin is obtained experimentally in the human heart by stimu-

5. Fahr, G.: Some Fundamental Principles of Electrocardiography, Arch. Int. Med. **27**:126 (Jan.) 1921.

6. Herman, G. R., and Wilson, F. N.: Ventricular Hypertrophy, Heart **9**:91, 1922.

7. Barker, P. S.; Macleod, A. G., and Alexander, J.: The Excitatory Process in Exposed Human Heart, Am. Heart J. **5**:720 (Aug.) 1930.

lating directly the right ventricle. If the latter views are correct, and there is reason to believe they may be so, the significance of the finding of right ventricular preponderance in bronchial asthma by Kahn and Unger is difficult to evaluate. In view of these considerations, and in view of the fact that preponderance is seen relatively so frequently in apparently normal persons, it appears that ventricular preponderance, per se, bears no important clinical significance in bronchial asthma and certainly does not indicate either cardiac strain or cardiac damage.

The cardiac measurements are taken from roentgenograms of the chest made at a distance of 6 feet in order to demonstrate any possible enlargement of the heart and particularly of the right side of the heart.

These measurements are compared with standard normal measurements for sex, height and weight, according to the tables of Claytor and Merrill, as quoted by Vaquez.[8] With the exception of only four patients who showed a slight increase in the transverse diameter, the cardiac measurements of the series studied are found to be well within the normal limits.

It is thus seen that patients with bronchial asthma exhibit neither symptoms nor physical findings suggestive of organic heart disease. On the laboratory side, there are no vital capacity, venous pressure, electrocardiographic or roentgenologic changes to suggest cardiac damage or heart failure. Furthermore, the literature affords no evidence of pathologic changes in the hearts of asthmatic patients who came to autopsy.[9]

THE HEART DURING THE ACUTE ASTHMATIC ATTACK

Since the symptoms of bronchial asthma are due to mild asphyxia, and since patients who die of an attack die of acute asphyxia, it is logical to expect that functional cardiac changes might occur during the acute attack that would be less extensive but nevertheless comparable to those seen in lower animals dying of anaphylaxis. Anaphylaxis when fatal in the guinea-pig is due to asphyxia which results, very much as in bronchial asthma, from closure of the bronchi and bronchioles so that expiration is not possible. I reported[10] that electro-

8. Vaquez, H., and Bordet, E.: The Heart and the Aorta, New Haven, Yale University Press, 1920, pp. 28-29.

9. Kountz, W. B., and Alexander, H. L.: Death from Bronchial Asthma; Three Cases, Arch. Path. **5**:1003 (June) 1928. Pollack, M.: Bronchial Asthma with Case Reports and Post Mortem Records, U. S. Vet. Bur. M. Bull. **4**:214 (March) 1928. Rackemann, F. M.: Fatal Asthma: Report of Case with Autopsy, Boston M. & S. J. **194**:531 (March 25) 1926. Huber, H. L., and Koessler, K. K.: The Pathology of Bronchial Asthma, Arch. Int. Med. **30**:689 (Dec.) 1922.

10. Criep, Leo H.: Electrocardiographic Studies of Effect of Anaphylaxis on the Cardiac Mechanism, Arch. Int. Med. **48**:1098 (Dec.) 1931.

cardiograms taken of guinea-pigs in a state of fatal anaphylactic shock demonstrate profound changes in cardiac rhythm and conduction, changes that range from simple acceleration of rate, delayed conduction and various degrees of heart block to ventricular fibrillation and cardiac standstill. Many of the tracings show inversion of the T wave in lead 1 and 2, and are suggestive of the picture seen in coronary occlusion. These changes are not specific of anaphylaxis, as they occur also if asphyxia is artificially induced by clamping off the trachea. The conclusion is therefore reached that they are due chiefly to myocardial anoxemia.

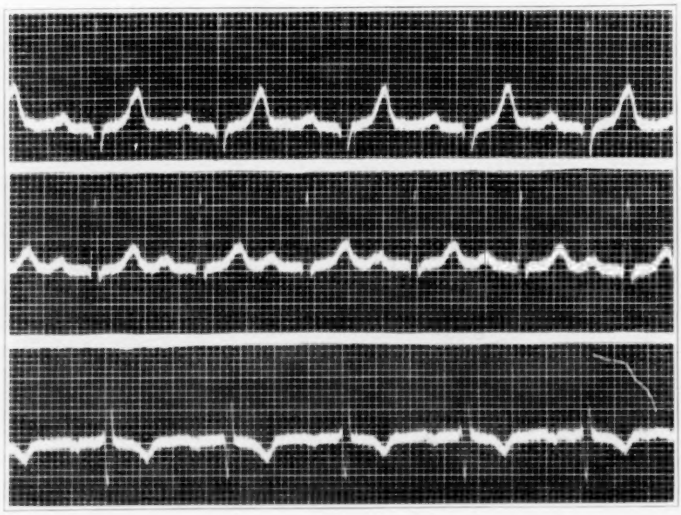

Fig. 6 (case 3).—Delays in A-V conduction during asthmatic attack. P-R interval, 0.24 second; three leads.

In order to demonstrate the effect of the acute asthmatic attack on the heart, twenty cases are reported. Of these, electrocardiograms were available in eight, while in twelve careful note was made of the pulse as regards its rate and rhythm. In the latter group, one patient showed clinically premature beats which occurred throughout the attack and for several hours following it. The other eleven patients showed no arrhythmia. Of the eight patients of whom electrocardiograms were made during the paroxysm (table 1), six were normal and two presented definite functional disturbances. One of these, case 3, showed definite delay in auriculoventricular conduction (fig. 6). This patient was a young adult the duration of whose asthma was sixteen years. An electrocardiogram taken during the asthma-free period showed only left

ventricular preponderance and normal conduction time. The tracing shown in figure 6, taken during a prolonged and severe attack, shows a P-R interval of 0.24 seconds, and this finding continued to be present for several days following the cessation of the acute symptoms.

The second patient, case 8, was a man, aged 22, who had had asthma since childhood. He also had hay fever, being highly sensitive to ragweed, and a very serious constitutional reaction developed ten minutes following treatment with ragweed extract. This reaction was characterized by urticaria, hay fever, asthma seizure and signs and

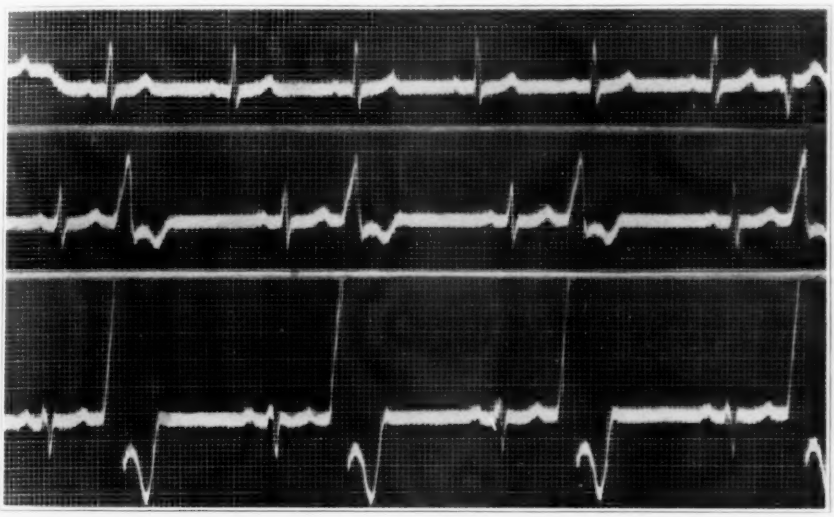

Fig. 7 (case 8).—Electrocardiogram taken during severe constitutional reaction. Mild sinus arrhythmia; premature beats of right ventricular origin; left ventricular predominance.

symptoms of suffocation and circulatory failure. An electrocardiogram obtained at this time (fig. 7) showed an occasional premature beat in lead 1, followed by premature beats of right ventricular origin occurring regularly after every other normal beat. This patient received 0.4 cc. of epinephrine hydrochloride fifteen minutes previous to the taking of the electrocardiogram, but it is unlikely that the epinephrine hydrochloride was responsible for these findings; the drug did not produce premature beats in other asthmatic patients, and at least one patient on whom a report is made in this paper showed premature beats before he received epinephrine hydrochloride.

It is true that the changes shown by both of these patients were very slight. At the same time, they were definite and seemed to be more or less directly connected with, if not actually caused by, the asphyxia of the asthmatic attack. The more advanced disturbances of rhythm that are observed in anaphylaxis and asphyxia in lower animals are not seen in clinical asthma, because the process is not sufficiently severe in the human being to cause such an analogously profound asphyxia. On the basis, however, of the foregoing findings, the opinion is ventured that electrocardiographic studies in fatal cases of asthma would show cardiac changes similar to those in fatal anaphylaxis.

SUMMARY

1. A complete cardiovascular survey of fifty patients suffering from bronchial asthma is presented.

2. An electrocardiographic study of the acute asthmatic attack in eight patients is reported.

CONCLUSIONS

1. Bronchial asthma does not have a permanent damaging effect on the cardiovascular system.

2. Acute attacks may as a result of the associated asphyxia produce minor transitory disturbances in cardiac conduction.

1004 May Building.

PSITTACOSIS

WITH RESULTS OF POSTMORTEM EXAMINATION IN A CASE INCLUDING STUDIES OF THE SPINAL CORD*

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AND
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The following case is reported, firstly, because, as far as could be ascertained, it is the first case of psittacosis in New York City in which the diagnosis was confirmed both by bacteriologic and by postmortem examination, and secondly, because the case permitted of studies on the changes in the spinal cord.

REPORT OF CASE

B. H., aged 51, a white woman, Jewish, a housewife, was admitted to the Jewish Hospital of Brooklyn to the private service of Dr. Meyer Rabinowitz on Feb. 5, 1931. The chief complaints were chills and fever for the last two days and pain in the back for the last four days.

Present Illness.—About a week before admission the patient was seized with intermittent chills. A physician was called and diagnosed her condition as "grip." The following day the patient felt improved, but three days later she developed signs of pneumonia and was taken to the hospital.

History.—The history was unimportant except for dyspnea on exertion. A brother died of "pneumonia" the previous week at the age of 65.

Physical Examination.—The patient lay quietly in bed and presented a definite malar flush and cyanosis of the lips and fingertips. The temperature was 105 F. The pulse rate was 116, and the respirations numbered 60 per minute. The blood pressure was 140 systolic and 70 diastolic. The pupils were equal and contracted, and failed to react to light. The ears, nose, throat and cervical lymph nodes were normal.

Examination of the chest showed limitation of expansion, dulness on percussion and moist râles over both bases, with tubular breathing above these areas. The patient did not complain of any chest pain. The heart showed no changes other than a rough systolic murmur at the apex.

The abdomen was moderately distended. On the day of admission the patient had five bowel movements. (The diarrhea persisted throughout her illness.)

February 6: The patient developed a hacking cough without expectoration, but was moderately comfortable in an oxygen tent. Respirations were mainly abdominal and at the rate of 30 per minute. Cyanosis persisted. The pulse rate was 112 (occasionally irregular), and respirations numbered 27 per minute. The temperature fluctuated between 104 and 105.8 F., and the blood pressure was 166 systolic and 70 diastolic. There was still absence of pleuritic pain.

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* Submitted for publication, April 25, 1931.

* From the Department of Pathology, the Jewish Hospital.

February 7: A pleural rub over the right anterior part of the chest was heard for the first time. Crepitant râles were heard over the upper left and entire right side of the chest posteriorly up to the apex, while over the lower lobe of the left lung there was now more resonance, indicating a regression of the process below with extension to the apex.

It may be of interest to note that the changes indicating a progressive ascending process from base to apex has been observed previously and referred to by Peterson as a creeping pneumonia.

February 8: No appreciable change in condition was noted.

February 9: The patient showed a definite decline. The pulse was irregular, the abdomen was distended, the respirations were shallow and rapid and the cyanosis was more marked. The patient became delirious and showed marked twitching of the face and extremities.

In the afternoon of the same day a reappearance of crepitant râles was noted over the base of the left lung, apparently a secondary infection. Numerous fine râles were also heard over the entire right side of the chest. The occasional hacking cough persisted, but remained unproductive.

February 10: The delirious state and abdominal distention were more severe, and the patient expelled large amounts of watery and foul fecal matter. Repeated examinations of the stool for blood and parasites gave negative results.

February 14: A spinal tap was performed, and 15 cc. of opalescent fluid under pressure was removed.

February 16: The abdominal distention increased, and the bowel movements continued foul and watery. The cyanosis became more marked and the respirations were very rapid (50 per minute) and labored, becoming gasping in character. The pulse became imperceptible, and death occurred at 9 a. m.

About five days after the patient's admission to the hospital the following information was obtained: Her brother (B^1) and his neighbor (F) had recently returned from Havana with six parrots. One of these parrots died on board the ship. The neighbor took the dead parrot and one of the live ones home with him. Shortly afterward, however, the second parrot also died. Of the remaining four birds, a pair (male and female) were taken by each of the patient's two brothers (B^1, B^2). The male bird of one and the female of the other of these two pairs flew away and the older (B^2) of the two brothers took the remaining two birds for mating purposes. He soon became ill and died of "pneumonia" (now believed to be of psittacosis origin) five days after the onset of the disease. One of the birds of the remaining pair also became ill and died during the course of its owner's illness. Then in rapid succession each of the following persons became ill: the sister (H) of B^2, whose case is here reported, two of his daughters (S and G) and the wife of his brother, who originally brought the birds from Havana and who for a time shared one of the birds of the last pair. They all had been at the home and had attended the funeral of the first victim. All were admitted to the hospital and all recovered except the patient whose case was just described. Two of the survivors (S, Mrs. B^1) had an uncomplicated course while the third (G) was still in the hospital at the time of this writing, recovering from the effects of a pulmonary embolus complicating convalescence.

Laboratory Data.—The urine showed traces of albumin and occasional red and white blood cells. Study of the blood revealed: red cells, 4,490,000, with 0.5 per cent reticulation; white cells, 10,800; polymorphonuclear neutrophils, 86.5 per cent, with 45 per cent nonsegmented forms; lymphocytes, 11 per cent; monocytes, 1.5 per cent; neutrophilic myelocytes, 0.5 per cent; metamyelocytes, 0.5 per cent;

platelets, 150,000 per cubic millimeter; hemoglobin, 64 per cent (Dare); color index, 0.7 per cent; bleeding time, 10 seconds, and coagulation time, 10 minutes. Repeated examination gave similar results. Blood taken for culture on February 6 was reported sterile after three days' incubation. The spinal fluid was under increased pressure and opalescent owing to the presence of numerous red blood cells. Albumin and globulin were present. Fehling's solution was reduced. The Wassermann test was negative. Colloidal gold was not reduced.

Fig. 1.—Surface of consolidated lung showing the typical smooth pleura.

Autopsy.—The body was that of an obese white woman. The external appearance showed nothing remarkable. The skin and mucous membranes showed no changes. The panniculus was thick. The muscles were bluish red and well developed.

Cavities: In the peritoneal cavity firm adhesions bound the transverse colon to the gallbladder. The pleural and pericardial cavities were normal.

The macroscopic examination showed certain conditions. Larynx: There was edema of the entire submucosa. Hemorrhagic areas were found in the epiglottis and just below the vocal cords. Trachea: Changes similar to those noted in the larynx were observed. Bronchi: The larger bronchi showed changes similar to those in the trachea.

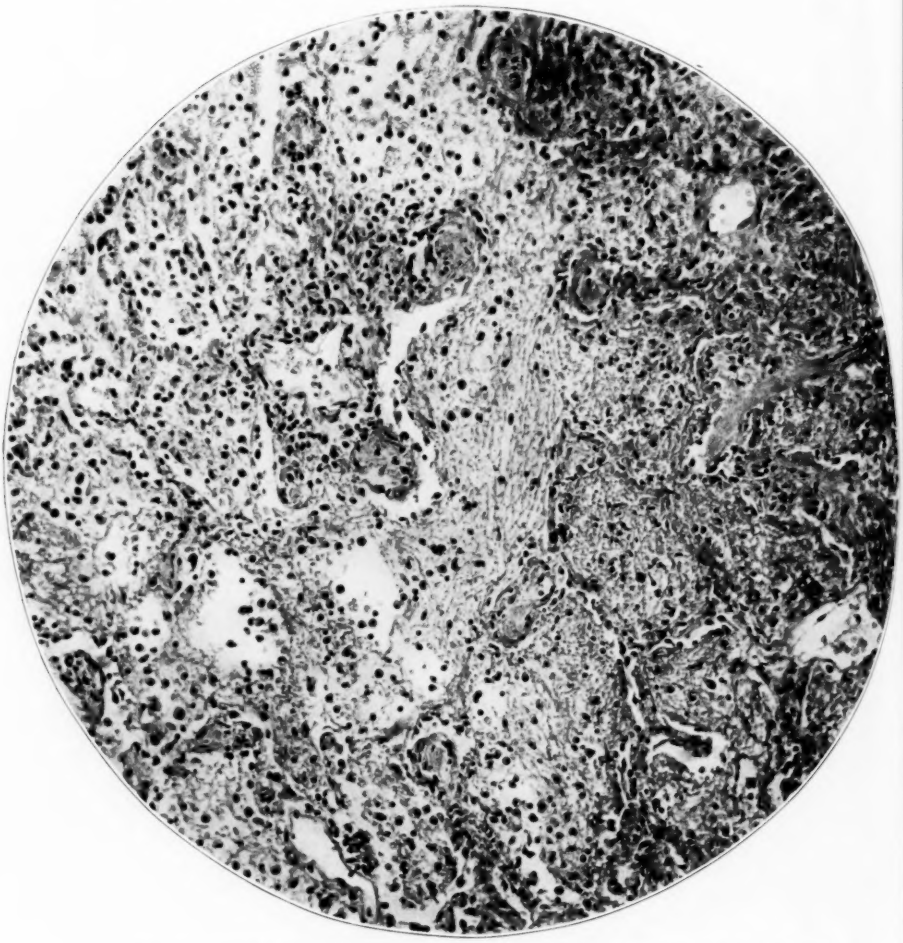

Fig. 2.—Section through the red area of consolidation showing fine and coarse fibrinous deposits in the alveoli and interalveolar septums; reduced from a magnification of 90.

Microscopic changes were also seen. Larynx: Congestion and edema were noted in the submucosa. Mononuclear, plasma and a few polymorphonuclear neutrophilic cells infiltrated this area. A thick layer of fibrin separated the zone of infiltration from the stroma beneath it. Trachea: Congestion and extravasation of blood

beneath the mucosa were observed. This process was accompanied by an infiltration with numerous polymorphonuclear, plasma and small as well as large mononuclear cells, the latter predominating. Bronchi: Examination of the right bronchus showed a marked congestion of the vessels throughout the entire depth of the wall. The latter was the seat of an infiltration similar to that noted in the trachea. Small

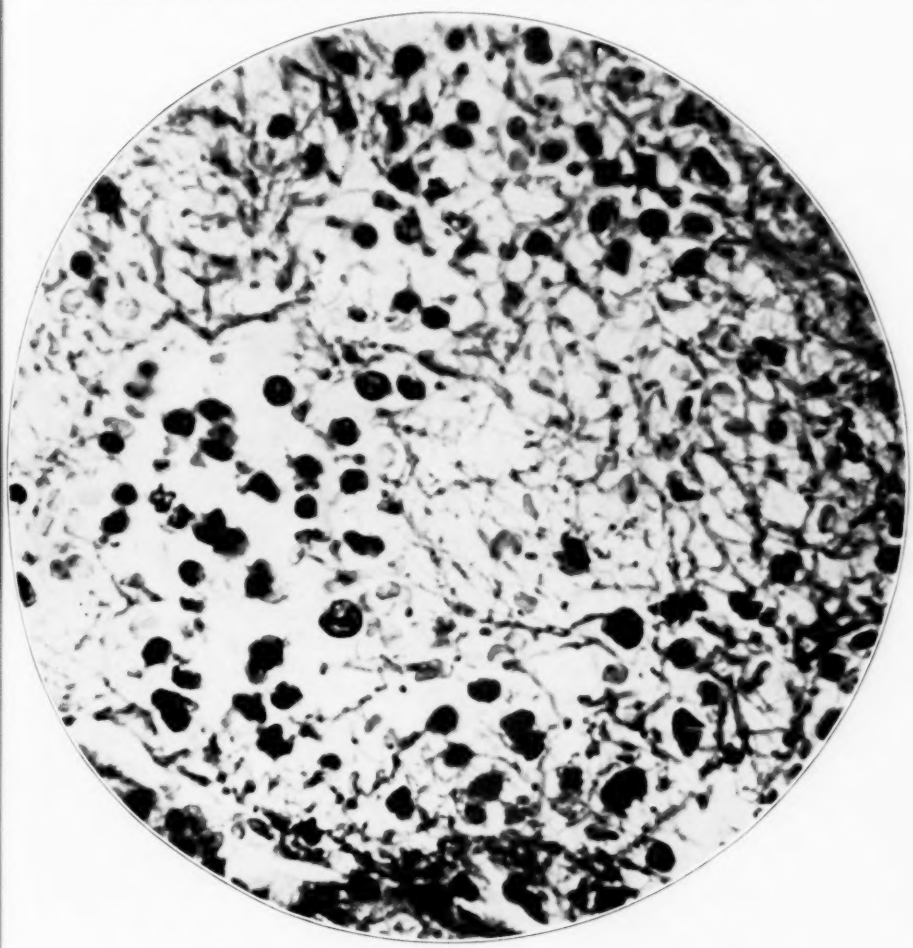

Fig. 3.—High power field showing the typical alveolar exudate consisting of large mononuclear cells, desquamated cells of the alveolar lining and plasma cells enmeshed in a fine fibrinous network. Polymorphonuclear leukocytes are absent.

mononuclear cells infiltrated the surrounding lung parenchyma. The left bronchus showed a similar but less marked involvement. The peribronchial lymph nodes were fibrosed and filled with anthracotic deposits. Numerous phagocytic cells and plasma cells were found diffusely infiltrating the interstices of the node.

Lungs: The right upper lobe was voluminous, firm in consistency throughout and bluish red, and had a smooth pleural surface (fig. 1). Section showed a uniformly dense, glossy, grayish-blue parenchyma. Microscopic examination revealed marked congestion and edema of the alveolar walls. The interalveolar septums in some sections were thickened by a fibrinous network which extended into the alveolar spaces. This was quite striking. In many alveoli it was made up of extremely fine fibrils forming a very delicate intertwining network. In others, the deposit was quite thick with only a few cells enmeshed in it (fig. 2). In most of the alveoli of this section there were found many plasma cells and

Fig. 4.—Cut surface of consolidated lung showing areas of consolidation and large thrombi in the pulmonary arteries.

large mononuclear cells, some of which had apparently been actively engaged in phagocytosis. Desquamated cells of the alveolar lining and large, pale vacuolated cells simulating ring forms were also scattered throughout the fibrinous network in the alveoli. Polymorphonuclear leukocytes were extremely scarce, and in many sections entirely absent. The alveolar epithelium was markedly hypertrophied and proliferative (fig. 3).

The right middle lobe showed similar parenchymal changes and, in addition, presented numerous thrombi plugging the blood vessels (fig. 4). Microscopic examination showed the bronchial walls to be markedly infiltrated with mononuclear and plasma cells. The alveoli showed changes similar to those already noted, and many of the pulmonary vessels were plugged by platelet thrombi. The epithelia

of the bronchial mucosae were almost entirely desquamated. The arteries showed markedly thickened medial coats. Many of the capillaries contained hyaline thrombi.

The right lower lobe macroscopically showed a more intensely red discoloration, although here also the bluish-gray patches were found occupying large areas of pulmonary parenchyma. Microscopic examination of the tissue showed a more pronounced hemorrhagic infiltration of alveoli as well as of alveolar septums.

The left upper lobe showed old adhesions which obliterated the interlobar fissure. Cut section showed irregular gray raised rough patches, some discrete and others conglomerated, scattered throughout the parenchyma. The larger patches were situated near the interlobar adhesions. Microscopic examination showed a process similar to that described in the right lung.

The left lower lobe showed similar but less extensive involvement. Microscopic examination showed changes essentially like those already noted, except for more abundant fibrin deposits in the involved alveoli. Areas of emphysema were found in the superficial portions of all lobes.

The left main pulmonary artery contained a large gray thrombus which was not adherent to the vessel wall and which on microscopic examination showed the typical architecture of a platelet thrombus. The smaller pulmonary arteries also contained gray thrombi.

Cardiovascular System: The heart weighed 380 Gm. The epicardium was normal, and the myocardium edematous. The left ventricular myocardium was markedly hypertrophied. The mitral valve consisted of three leaflets, the accessory one being about one-half the size of the other two. Hemorrhagic areas were found in the endocardium of the mitral, tricuspid and aortic leaflets. The foramen ovale was partially patent. The coronary arteries were normal. Microscopic examination showed swelling of the muscle cells throughout. Sections through the posterior wall of the left ventricle showed small discrete foci of polymorphonuclear and plasma cell infiltration between muscle cells. The tricuspid valve in the region of the hemorrhagic area noted on gross examination was the seat of a subendocardial extravasation of red cells. The middle aortic cusp showed a marked subendocardial fibrin deposit.

The aorta and other large arteries showed a moderate atherosclerosis macroscopically and microscopically.

The right iliac vein was occluded by a gray thrombus, not adherent to the vessel. Microscopic examination of the vein showed a typical platelet thrombus with no change in the vessel wall. Numerous cocci were found in the thrombus.

Gastro-Intestinal Tract: The entire wall of the esophagus was edematous and the mucosa was the seat of areas of marked congestion. Microscopic examination showed markedly congested vessels beneath the mucosa with an infiltration by plasma cells and occasional large mononuclear cells.

The cardiac portion of the stomach mucosa was extremely hemorrhagic. The pyloric portion was polypoid and less hemorrhagic. Microscopic examination showed extravasation of blood in the mucosa of the cardia and congestion of the entire submucosa.

There were numerous mucosal hemorrhages in the small as well as the large intestines. Dense adhesions bound the ascending colon to the gallbladder. The lymph follicles of the intestines showed no changes. Microscopic examination showed no abnormalities other than congestion of the vessels and occasional areas of infiltration with large mononuclear cells.

Biliary Tract: The liver weighed 2,550 Gm. The capsule was smooth and glistening. The consistency was firm. The color was pale reddish brown with

yellow mottling. The architecture was clouded. The main portal vein was normal, but its right branch was reduced to a fibrous cord, containing no visible lumen. The left branch was of large caliber, and as it entered the deeper portion of the parenchyma it gave off branches to the right lobe. Section through the right lobe of the liver through the altered right branch of the portal vein showed the tissue in that region to be the seat of a gray scar. One of the smaller vessels passing through this area contained a thrombus, apparently of recent origin. The biliary channels were normal. The hepatic veins were normal. The bed of the gallbladder was the seat of dense adhesions that bound the organ to the under surface of the liver. Microscopic examination showed a marked fat replacement with only a few small areas of normal liver parenchyma. The distribution of the fatty changes was central as well as periportal. This was accompanied by a periportal small round cell infiltration. There was also a marked bile pigment deposit in many of the liver cells. Section through the scar showed platelet thrombi in the large branches of the portal vein. The liver tissue in this region was completely replaced by a scar, and the surrounding hepatic parenchyma was markedly replaced by fat.

The gallbladder was embedded in a mass of adhesions which bound it to the hepatic flexure of the colon. The wall of the organ was markedly thickened and pearl gray. Its lumen was occluded by several large bile pigment calculi. The rugae of the mucosa were hypertrophied, and in areas adhered to each other to form separate pockets containing inspissated bile. The cystic duct was normal except for a thickening of its wall. Microscopic examination showed a marked fibrosis of the organ.

The pancreas weighed 100 Gm. It was firm in consistency and on section; the head of the organ presented a small pearl-gray discrete nodule. Microscopic examination revealed a pronounced interstitial fibrosis. The nodule was found to consist of a large island of dark-staining epithelial cells, irregularly scattered, although some of them showed a tendency to alveolar and ductlike structure. This nodule was completely circumscribed by a dense fibrous capsule.

The spleen weighed 400 Gm. The capsule was smooth. The color was reddish purple and the consistency extremely soft. Cut section showed a semifluid jelly-like splenic parenchyma. The splenic vein was occluded by a large gray thrombus which was unattached to the vessel wall. Microscopic examination showed a marked extravasation of blood in the pulp throughout the organ. Scattered throughout the parenchyma were found numerous large mononuclear and plasma cells. The splenic follicles were obscured by the hemorrhagic process and reduced in size and number. The venous sinuses were engorged with blood and pigment. The arteriolar walls were thickened.

Each suprarenal gland weighed about 10 Gm. In both organs there was cloudy swelling and the medullary portions showed softening and red discoloration. Microscopic examination showed a marked autolysis of the parenchyma and congestion of the medulla in each organ.

Genito-Urinary System: The left kidney weighed 250 Gm.; the right, 275 Gm. The capsules stripped with slight difficulty, leaving a rough bluish-gray surface with numerous cortical cysts of varying size. On the surface of the left kidney there was a small stellate scar. Section through the organ showed a cloudy swelling of the parenchyma. The larger vessels showed thickening of their walls. The pelves were markedly hemorrhagic and edematous. Microscopic examination showed congestion of the glomerular tufts and slight granular degeneration of the tubular epithelium. The pelvis was edematous and the seat of marked extravasations of blood. The stellate cortical scar noted in the left kidney was the seat

of an infiltration with mononuclear cells and a marked fibrosis that replaced the glomeruli and tubules of the involved portion of kidney.

The ureters were normal. The bladder was normal except for edema of its wall.

Fig. 5.—High power field in anterior horn of the spinal cord showing changes in the morphology of the neurons and hemorrhages.

The uterus was the seat of intramural and subserous fibroids. The endometrium was hemorrhagic and polypoid. Microscopic examination showed a marked polypoid hyperplasia of the endometrium and cystic changes of the glands of the cervical mucosa. The fibroids in the wall of the uterus presented areas of cystic degeneration. The fallopian tubes showed congestion on gross and microscopic examination. The ovaries were slightly enlarged and the seat of small

cysts, some of which contained clear yellow fluid; others, bloody fluid. Microscopic examination showed follicular cysts, some filled with extravasated blood.

Thyroid: The left lobe was the seat of a thick-walled cyst. The right lobe was normal. Microscopic examination revealed the presence of a fetal adenoma and a cystic degeneration of the left lobe. The right lobe was normal.

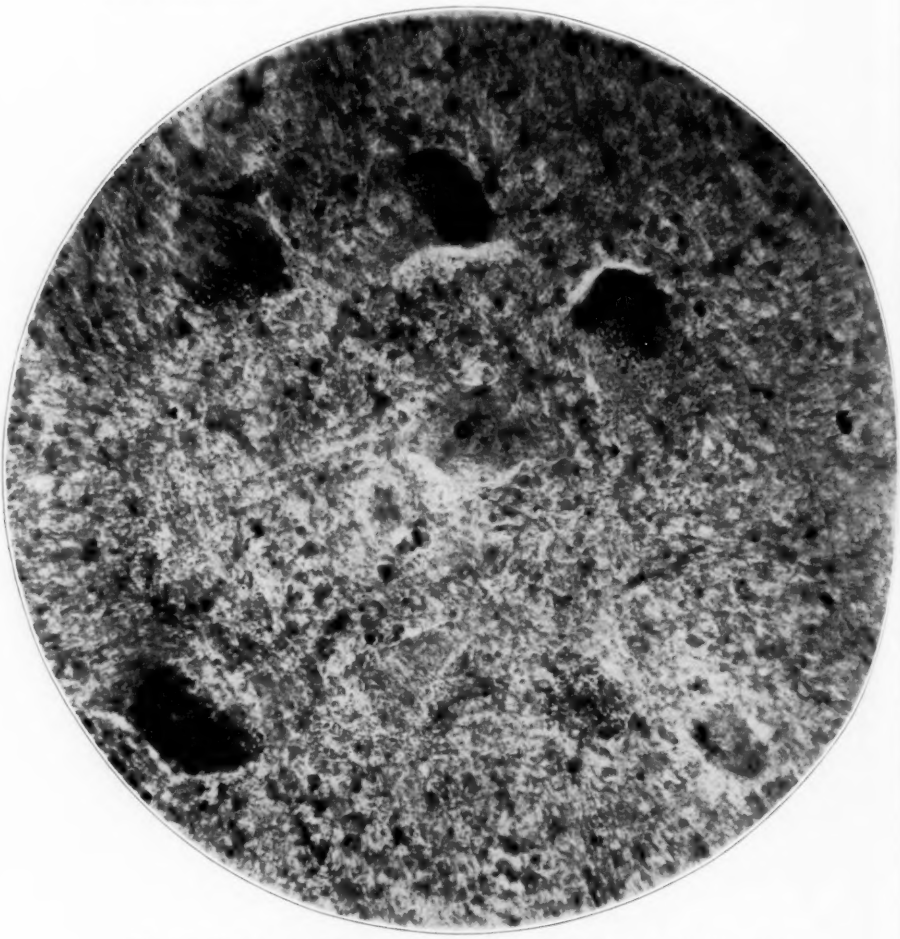

Fig. 6.—High power field of anterior horn of the spinal cord, showing fat droplets in neurons; sudan III.

Thymus: This was almost completely replaced by fat. Microscopic examination showed almost complete replacement of the thymic structure by fat and lymphocytes.

Ribs and Vertebrae: These were normal. The rib marrow was red and on microscopic examination showed a hyperplasia of all elements.

Examination of the brain was not permitted.

Spinal Cord: The dura mater was moderately congested. The pia mater, especially in the region of the lumbar segments, showed a more marked congestion of vessels. Transverse section of the spinal cord revealed a yellowish discoloration of the right posterior horn. Microscopic examination of celloidin and paraffin preparations with various stains showed the following: With hematoxylin and eosin stain there was a moderate amount of chromatolysis of the anterior horn cells and an increase in the glial cells. Some of the neurons showed other morphologic changes, consisting of a transformation of the usual pyramidal form into rounded or otherwise distorted shapes and an eccentric position of the nuclei, some of which took the stain very faintly or not at all. Here and there were noted areas of perivascular round cell infiltration. The vessels were congested throughout the gray and white matter. In the anterior horns were found several hemorrhagic areas. The extravasation seemed to follow the course of blood vessels in some places, although no break in the structure of the latter could be demonstrated (fig. 5). In preparations stained with sudan III, fat droplets were found in abundance in most of the nerve cells of the anterior horns (fig. 6). With cresyl-violet, the chromatolysis and morphologic changes in the neurons noted in the sections stained with hematoxylin and eosin were more definitely visualized. In Weil preparations myelin degeneration could not be demonstrated. With van Gieson's method there was no increase noted in the fibrous tissue of the meninges or cord. With Davenport's stain the increase in neuroglia and changes in the neurons already noted were again clearly demonstrated.

Although the changes described were definite they cannot be considered characteristic of this disease, since similar changes in the spinal cord may occur in toxic states other than those associated with psittacosis.

Bacteriologic Examination.—Tissue from the lung, liver and spleen, secured under aseptic precautions, was submitted to Dr. G. P. Berry of the Rockefeller Institute for bacteriologic study. Dr. Berry reported that he identified and isolated the psittacosis virus from each of these tissues. He also isolated the virus from the sputum of one of the survivors (Mrs. B[1]) and from the liver and spleen of the last remaining parrot received from the home of one of the survivors (S). (Without the work done by Dr. Berry a definite bacteriologic diagnosis of psittacosis could not have been established in this case.)

COMMENT

A considerable amount of literature has recently been published dealing with the various phases of this interesting disease. To avoid repetition, therefore, only the pertinent facts concerning this subject will be reviewed, omitting the clinical aspects which will be the subject of a subsequent publication by Dr. Meyer Rabinowitz.

In the epidemiologic report on psittacosis published by the League of Nations,[1] this disease is defined as one due to an unknown patho-

1. Roubakine, A.: Monthly Epidemiological Report of League of Nations, no. 4, 1930 (an excellent review with full references).

genic agent, and transmitted to man by certain species of parrots and especially by parrots from the Amazon.

The disease was first described by Jurgensen,[2] in 1876, as an atypical pneumonia of animal origin. The first recognized epidemic occurred in and around Paris and Switzerland in 1879, and was described by Wagner[3] and by Ritter and Uster,[4] respectively. All victims had been in contact with sick parrots from tropical countries. Since then epidemics have occurred in various parts of the world at frequent intervals. There was an epidemic in Bonn in 1882, in Leipzig in 1886, in Paris in 1892 and 1896, in Italy in 1894, in Berlin in 1898, in Brazil in 1904, in New Hampshire in 1904, in Zulprich (Rhineland) in 1909, in England in 1914, in Wilkes-Barre, Pa., in 1917, in Edinburgh in 1924, in Pennsylvania again in 1928 and in England again in 1929. Up to the end of 1929, there occurred, according to Heymann,[5] a total of 164 cases, with 54 deaths. Between the end of 1929 and the beginning of 1930, however, much more severe epidemics occurred in the following locations: Argentina, Germany, England, Austria, Czechoslovakia, the Netherlands, Denmark, Switzerland, Poland, Spain, Portugal, Algeria and, last but not least, the United States of America. In this country outbreaks occurred in sixteen states, including the Hawaiian Islands. During these few months about 400 cases of psittacosis were reported throughout the world and more than one fourth of these occurred in the United States.

All the cases reported in this country were traced to one or two consignments of parrots from South America, so that on Jan. 4, 1930, the President was forced to prohibit the import of parrots into the United States. Since then, however, sporadic cases and epidemics have been reported in this country. McCoy[6] reported the cases of several laboratory workers from the Hygienic Laboratory of Washington, D. C., who were afflicted with the disease after exposure to infected parrots with which experiments were being carried out. Gorham, Calder and Vedder[7] reported cases in New York State, Haines[8] in Ohio, Bortz and Green[9] in Pennsylvania, Wirth[10] in New Orleans,

2. Jurgensen, in von Ziemssen: Handbuch der allgemeinen Therapie, Leipzig, F. C. W. Vogel, 1874.

3. Wagner: Der sogenannt Pneumotype, Deutsches Arch. f. klin. Med. **35**: 191, 1884; **42**:405, 1888.

4. Ritter and Uster: Deutsches Arch. f. klin. Med. **25**:53, 1880.

5. Heymann, B.: Klin. Wchnschr. **5**:193, 1930.

6. McCoy, G. W.: Pub. Health Rep. **45**:843, 1930.

7. Gorham, L. W.; Calder, F. G., and Vedder, J. D.: Psittacosis, J. A. M. A. **94**:1816 (June 7) 1930.

8. Haines, H. G.: Psittacosis, J. A. M. A. **94**:1821 (June 7) 1930.

9. Bortz, E. L., and Green, B.: Psittacosis, J. A. M. A. **95**:400 (Aug. 9) 1930.

10. Wirth, W. R.: New Orleans M. & S. J. **83**:132, 1930.

Rivers, Benjamin and Berry [11] in New York (another case resulting from contact with sick parrots in the laboratory during experimental investigations), Maclachlan, Permar and Rogers [12] in Pittsburgh, Peterson Spalding and Wildman [13] in Washington, Wellman [14] in Massachusetts, Sandoer and Coburn [15] in Kansas, Hahn [16] in Connecticut and Badger [17] in a department store of a certain city in the United States, the name of which is not stated.

The greatest number of cases have been caused by contact with the Brazilian green parrot known as the Amazon parrot. The disease, however, has been shown to be transmitted also by the gray parrot of Africa, love-birds, canaries, thrushes and the Italian cardinal bird. Psittacosis may also be contracted by domestic fowls, mice, bullfinches, rabbits and even cats.

Those familiar with the conditions of the trade in parrots are of the opinion that the poor conditions of transportation and the change in climate and general environment [18] of these wild birds light up a latent psittacosis infection and make them ready hosts for the disease.[19] It is not known, however, how long a newly imported parrot may be a potential source of danger.

Direct contact with the infected animal is not the only way in which the disease may be contracted. Infection by fomites is a recognized possibilty. This is supported by the case described by Horder and Gow.[20] Human transmission of the disease is also possible, according to some investigators. Such cases have been reported by Hegler,[21] Kerschensteiner,[22] Stefanopoli,[23] Cosman [24] and Sturdee and Scott.[25]

11. Rivers, T. M.; Benjamin, B., and Berry, G. P.: Psittacosis, J. A. M. A. **95**:577 (Aug. 23) 1930.

12. Maclachlan, W. W. G.; Permar, H. H., and Rogers, C. A.: Ann. Int. Med. **4**:260, 1930.

13. Peterson, E.; Spalding, O. B., and Wildman, O.: Psittacosis, J. A. M. A. **95**:172 (July 19) 1930.

14. Wellman, H. E.: New England J. Med. **203**:421, 1930.

15. Sandoer, S. A., and Coburn, C. E.: J. Kansas M. Soc. **31**:28, 1930.

16. Hahn, T. F., Jr.: Yale J. Biol. & Med. **2**:417, 1930.

17. Badger, L. F.: Pub. Health Rep. **45**:1403, 1930.

18. Gordon, M.: Proc. Zool. Soc. Lond., 1928, pt. 2.

19. Parrots in Brazil in Relation to Psittacosis, Correspondence, J. A. M. A. **95**:876 (Sept. 20) 1930.

20. Horder, T., and Gow, A. E.: Lancet **1**:442, 1930.

21. Hegler, C.: Deutsche med. Wchnschr. **4**:148, 1930.

22. Kerschensteiner: München. med. Wchnschr. **77**:310, 1930.

23. Stefanopoli: Bull. san. de l'Algérie **387**:54, 1930.

24. Cosman, quoted by Stefanopoli (footnote 23).

25. Sturdee, E. L., and Scott, W. M.: A Disease of Parrots Communicable to Man (Psittacosis), Ministry of Health, Reports on Public Health and Medical Subjects, no. 61, London, His Majesty's Stationery Office, 1930 (another excellent review with an extensive bibliography).

There are several facts, however, that argue against psittacosis being a disease that may be spread from man to man. In the first place, the outbreaks do not assume real epidemic forms as do, for instance, those of influenza. They affect only household or family groups; in most cases contact with sick parrots can be proved. Secondly, the occurrence of epidemics coincides exactly with the import of a consignment of sick parrots and diminishes with the prohibition of their importation, ceasing entirely after all the sick parrots have died. Thirdly, it is difficult to ascertain beyond doubt that a given patient did or did not have contact with a sick parrot.

In reviewing the literature on the bacteriology of this disease one finds that numerous organisms have been associated with it. Thus, in 1888, Finkler [26] associated a streptococcus with this disease. In 1892 Netler and Gastou [27] demonstrated a pneumococcus in their cases. In 1893 Nocard [28] described the Bacillus psittacosis which he found in the marrow of parrots and in the wings of parrakeets that died of this disease. This was later confirmed by Gilbert and Fournier,[29] who found the same organism in the heart's blood of one of his patients. In 1920, Peney [30] isolated from a parrot with psittacosis another similar organism, Bacillus aetrycke, which he considered to be the etiologic agent. In 1928, Thomson [31] described as the cause of the disease another organism, similar to that described by Nocard. None of these, however, are today considered to be the cause of psittacosis because recently it seems to have been definitely shown that the malady is due to a filtrable virus. This was suggested by Bedson and his co-workers [32] in 1930. Since then, European as well as American investigators have confirmed the theory, and today the filtrable virus is accepted by most workers [33] to be the causative agent. It may also be added that Lillie [34] has reported finding certain minute, coccoid and bipolar, gram-negative, bacilliform inclusion bodies (Rickettsia psittaci) in the phagocytic cells of the alveolar exudate and in mononuclear cells of the alveolar walls.

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26. Finkler, Z.: Kongr. f. inn. Med., 1888.

27. Netler and Gastou, quoted by Sturdee and Scott (footnote 25).

28. Nocard, E.: Conseil d'hygiene du Département de la Seine, 1893.

29. Gilbert and Fournier, quoted by Dubief: Nouveau traité de médecine et de thérapeutique, Paris, 1920, no. 1, p. 306.

30. Peney, H. M.: Brit. J. Exper. Path. **1**:131, 1920.

31. Thomson, A. P.: Practitioner **124**:377, 1930.

32. Bedson, S. P.; Western, G. T., and Simpson, S. L.: Lancet **1**:235, 1930.

33. Rivers, T. M.; Berry, G. P., and Rhoads, C. P.: Psittacosis, J. A. M. A. **95**:579 (Aug. 23) 1930. Krumwiede, C.; McGrath, M., and Oldenbusch, C.: Science **71**:262, 1931. Gordon, M. H.: Lancet **1**:1174, 1930. Armstrong, C.; McCoy, G. W., and Branham, S. E.: Pub. Health Rep. **45**:725, 1930.

34. Lillie, R. D.: Pub. Health Rep. **45**:773, 1930.

These bodies have been found to be associated with psittacosis, not only by the original observer but also by Levinthal,[35] Coles [36] and others.

The clinical picture in psittacosis points to the involvement of two systems especially, namely, the respiratory and central nervous systems, represented by the pneumonia and the typhoid state respectively. Since the other organs show the usual changes found in general sepsis, only the most important observations concerning the pathologic changes in the lung and nervous system will be reviewed.

With regard to the pulmonary changes, there is some difference of opinion among pathologists. According to Oberndorfer,[37] the gross and microscopic observations in psittacosis are almost identical with those in influenzal bronchopneumonia. Confluent bronchopneumonia, bronchitis and bronchiolitis have been described by Hederschee [38] and

Points of Differentiation in the Pulmonary Pathology of Psittacosis and Influenza

	Psittacosis	Influenza
Type of consolidation	Lobar	Nodular, even when areas of consolidation become confluent
Cells lining the alveoli	Marked hyperplasia and hypertrophy	No marked change
Type of cellular exudate	Polymorphonuclear cells are absent or scarce; exudate consists of mononuclear, plasma and desquamated epithelial cells	Numerous polymorphonuclear cells, occasionally to the extent of suppuration
Relation of bronchi to areas of consolidation	None; bronchioles involved by extension of process from the surrounding lung tissue	Definite; capillary bronchitis with bronchopneumonia
Fibrin deposit	Very abundant throughout	Scarce, except near involved bronchioles
Character of hemorrhagic lesion	Associated with capillary thrombosis and severe necrosis of lung tissue	Not associated with either
Bacteria in the lung tissue	Scarce or absent except in areas of secondary infection	In large numbers throughout the lung

others as the basic change in the lungs in this disease. Contrary views, however, are held by most pathologists, including such authorities as Wilson [39] and Turnbull,[40] who found the changes to be, as Sturdee stated it, "different from anything they have previously seen."

Since so much controversy is centered about the resemblance between psittacosis and influenzal pneumonitis, it will perhaps be helpful, for purposes of emphasis, to tabulate the points of differences between these two conditions (see table).

35. Levinthal, W.: Klin. Wchnschr. **9**:654, 1930.
36. Coles, A. C.: Lancet **1**:1011, 1930.
37. Oberndorfer: München. med. Wchnschr. **77**:311, 1930.
38. Hederschee: Nederl. tijdschr. v. geneesk. **8**:873, 1930.
39. Wilson, G. H.: J. Path. & Bact. **33**:957, 1930.
40. Turnbull, quoted by Hutchison, R.; Rowlands, R. A., and Levy-Simpson, S.: Brit. M. J. **1**:633 (April 5) 1930.

Other less constant changes which may be of aid in recognizing the pneumonitis of psittacosis are the dark, purplish-blue color of the lung, the relative absence of pleural exudate and the occurrence of small subpleural hemorrhages.

The literature on the changes in the central nervous system in psittacosis is very scant, yet as was indicated, the clinical picture points to extensive involvement of this system; to wit, the photophobia, lethargy, stupor, sluggish speech, slow response, muttering delirium, incontinence, severe backaches, ataxia in convalescence and even localizing signs, such as facial immobility and muscle jerks. All these signs must be based on anatomic changes in either the brain or the spinal cord. Sturdee stated that congestion and edema in these organs are not infrequent findings. The references to studies on these organs, however, are very few. In one case studied by Oberndorfer, no changes were found in either the brain or the cord. Turnbull reported finding ring hemorrhages in the brain and cord in two of Hutchison's cases.[41] Hegler found multiple foci of softening in one case. Wilson found no brain lesions except atrophy of convolutions beneath a thickened and opaque pia-arachnoid. Hederschee found internal hemorrhagic pachymeningitis and a mixed coagulum in the sagittal sinus. Peterson found the following changes in one case in which he performed and autopsy: In the brain there was compression of the ventricles with marked dilatation of the veins along the septum and tela choroidea. The caudate nucleus contained large ring hemorrhages. The corpus callosum, internal capsule, putamen and thalamus were the seats of punctate hemorrhages. The hemorrhages showed a tendency to be elongated in the direction of the nerve fibers, with an occasional zone of necrosis in the center. There was also an infiltration with phagocytes and occasional lymphocytes and polymorphonuclear cells. Circumscribed areas of degeneration of myelin were also demonstrable. The spinal cord was not described.

These are the changes thus far uncovered in the nervous system for the neurologist to correlate with the clinical signs. How much these changes contribute to the cause of death is at present difficult to state. The vital centers of those dying with signs of marked central nervous system involvement may be sufficiently injured to be more than a mere contributory factor in the cause of death. In those who recover, however, there are apparently no residual neurologic changes, indicating that in these cases whatever injuries to the nerve tissue occurred were not permanent. It is obvious that in psittacosis the central nervous system needs much more careful study than it has been given heretofore.

41. Hutchison, R.; Rowlands, R. A., and Levy-Simpson, S.: Brit. M. J. **1**:633, 1930.

CONCLUSION

The results of postmortem and bacteriologic examination in a case of psittacosis are reported. This case was one of a household epidemic in which five were afflicted with the disease, with two deaths, and which was traced to contact with newly imported parrots that were found to be suffering from psittacosis.

The pathologic changes found in the lung and spinal cord are especially emphasized. The resemblance between the pneumonia of psittacosis and influenza being a controversial subject, the points of difference between these two conditions are tabulated. In view of the fact that the clinical signs in this disease point to marked involvement of the central nervous system, the changes in the latter are described in detail. The scarcity of information in the literature on this phase of the subject is pointed out and a plea is made for more studies on the changes in the central nervous system in psittacosis.

The history, epidemiology and bacteriology of psittacosis are briefly reviewed.

THE EFFECT OF NITRITES ON PAIN AND ON THE MOTILITY OF THE GASTRO-INTESTINAL TRACT

I. CLINICAL STUDY *

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That nitrites have some action on the gastro-intestinal tract was first called to my attention in July, 1926, when a patient, who was being treated in the hospital by the Sippy method for a duodenal ulcer, complained of precordial pain. The intern interpreted this pain as angina pectoris because he found a slight elevation of the blood pressure during these attacks. For this reason amyl nitrite was given to the patient to inhale. The pain was relieved promptly. During a subsequent attack of pain a duodenal tube was passed, and aspiration of the gastric contents, which were high in acidity, gave as prompt relief as the amyl nitrite. An increase in the dose of alkalis stopped the attacks.

This experience led me to investigate the effect of nitrites on the gastro-intestinal tract in other patients who were suffering with disease of the stomach and intestines.

METHOD

This study comprises two types of observations made on patients: (1) observations to determine the effects of nitrites on abdominal pain of gastric or intestinal origin and (2) observations to determine the action of these drugs on the motility of the stomach and intestines.

Observations were made on 60 patients having abdominal pain arising from the stomach or intestines: 20 with duodenal ulcers; 10 with gastric ulcers; 3 with pyloric stenosis; 20 in whom the only apparent cause of the pain was hypermotility, pyloric spasm or hyperacidity, and 7 with intestinal cramps.

Amyl nitrite, nitroglycerin and sodium nitrite were the preparations used. Amyl nitrite was used in most instances because it acted more promptly, and the dose giving the desired physiologic action was more readily controlled than it was with the other preparations. The amyl nitrite was administered by having the patient inhale the fumes of one or two "pearls" crushed in a piece of gauze. They inhaled the fumes until they complained of such subjective symptoms as throbbing in the

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* From the Medical Clinic of Lakeside Hospital and the Department of Medicine, Western Reserve University.

head, slight dizziness or a warm flush feeling, or until there were objective signs, such as a rapid pulse or a fall in blood pressure. This usually required from one-half to one minute's inhalation of the amyl nitrite.

Nitroglycerin was administered by placing the drops on the patient's tongue, beginning with 3 drops and increasing the dose by a drop every two minutes until symptoms showing a reaction to the nitrite appeared. The average dose required was about 7 or 8 drops.

The action of nitrites on the motility and tone of the stomach and intestines was studied by observing their effect on the gastro-intestinal tract during fluoroscopic examination. The same technic of administration was employed as has already been described. Observations were made on 200 persons, a group of normal individuals and on patients who showed hypermotility, spasm or some filling defect of the stomach or intestines.

In order to rule out the possible psychic action from the inhalation of amyl nitrite, observations were made on a group of patients after the inhalation of aromatic spirits of ammonia and amyl acetate. Ammonia was chosen because of the ease with which its penetrating odor produces reflex or psychic reactions. Amyl acetate was chosen because the odor is similar to that of amyl nitrite.

RESULTS

Amyl nitrite gave complete relief from pain in twelve of the patients with duodenal ulcer, partial relief in four and no relief in four. The pain was relieved for from five to twenty minutes. No explanation can be offered for the difference in the manner in which the patients responded to the amyl nitrite as all of them had simple duodenal ulcer without complications.

Six patients with gastric ulcer obtained relief of pain for from five to fifteen minutes after inhalation of amyl nitrite, whereas in four patients with penetrating gastric ulcer the pain was not controlled.

In three patients with pyloric stenosis proved by operation in whom visible peristalsis was observed, amyl nitrite not only relieved the pain but caused cessation of the peristalsis. The peristalsis disappeared more promptly than the pain but reappeared in from three to five minutes while the pain was relieved for from five to ten minutes.

In the patients showing only spasm or hypermotility to explain the gastric pain, amyl nitrite gave complete relief from pain for from fifteen minutes to two hours, and in seven patients with intestinal cramps the pain was relieved for from ten to twenty minutes.

The action of glyceryl trinitrate on the gastro-intestinal tract was observed in a small number of patients on whom the amyl nitrite studies

were made. The only difference in the action of these two drugs was that amyl nitrite acted more promptly, and the duration of relief from pain was shorter.

Sodium nitrite was given to eight patients with duodenal ulcer for a period of one week. The dose was 1 grain (0.065 Gm.) three times a day. None of these patients had relief from pain, although they responded to amyl nitrite and glyceryl trinitrate. Two patients having duodenal ulcer with pylorospasm who continued to have pain on alkaline therapy and diet, obtained relief with the administration of sodium nitrite, and had a return of pain when sodium nitrite was discontinued. In twelve patients with gastric pain in whom spasm and hypermotility were the only findings, eight obtained relief from pain with sodium nitrite, and four obtained no relief.

In the group of patients on whom fluoroscopic studies were done, the most constant action of nitrites on the gastro-intestinal tract was cessation of peristalsis and diminished tone (figure). Of two hundred persons on whom fluoroscopic observations were made, only ten failed to show some response to nitrites. Five of these had duodenal ulcer and five showed no organic lesion. The duration of action was from two to five minutes with amyl nitrite, and from five to ten minutes with nitroglycerin.

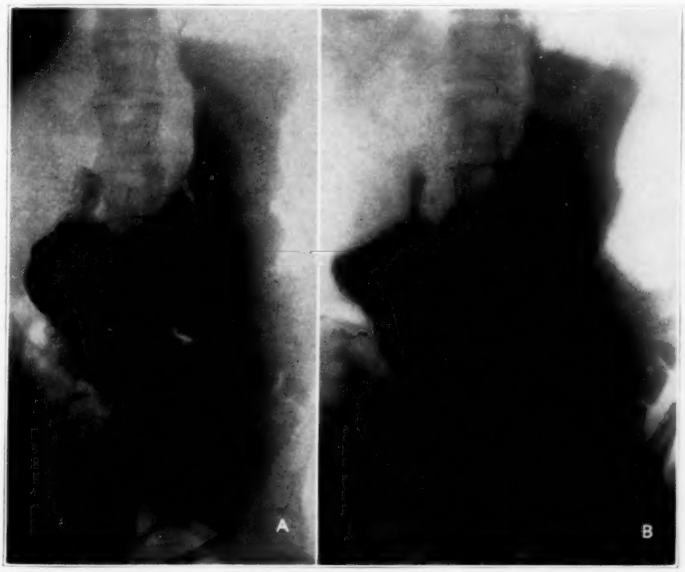
Deformities in the stomach or the intestines, the result of organic lesions, were unaffected; in fact, the deformity was accentuated when the uninvolved portion of the stomach or intestines relaxed. In several patients there were deformities of the gastro-intestinal tract which were not recognized until after amyl nitrite was administered. This was very well illustrated in a patient, 45 years of age, with a history of weakness, loss of weight and some distress after eating of three months' duration. The physical examination gave negative results, and the fluoroscopic examination revealed a slight unevenness in the upper third of the stomach, which was thought to be of no importance. After the administration of amyl nitrite, the peristalsis ceased and the stomach was more relaxed, except for this region which appeared then to be a definite deformity. Operation revealed carcinoma.

Only six patients were observed to have abdominal pain during fluoroscopic examination. In all these patients vigorous peristalsis was seen during the paroxysms of pain. Administration of amyl nitrite stopped the peristalsis and the pain simultaneously. Repeated trials were made during the course of the examination, with the same result.

Pylorospasm did not yield to nitrites as readily as might be expected. Only eight of seventeen patients who were observed with pylorospasm, showed relaxation when nitrites were administered. Six of these cases were extrinsic in origin, and two were presumably intrinsic, for there were deformities of the duodenal cap typical of duodenal ulcer.

Of the nine cases that were not modified by the nitrites, seven were extrinsic and two intrinsic in origin. Only three cases of cardiospasm were observed in this study; two of them showed complete relaxation, and one was not modified by the nitrite.

All the patients showing no relaxation of the pylorus or cardia in response to nitrites were subsequently observed after the administration of atropine, and it was found that atropine was no more effectual than the nitrites.



Roentgenograms showing the effect of amyl nitrite on the tone and peristalsis of the stomach. *A*, stomach showing active peristalsis. *B*, after the inhalation of amyl nitrite for one-half minute, peristalsis ceased and tone diminished.

There were twelve patients in whom fluoroscopic examination of the colon showed obstruction to the passage of barium or marked spasticity that was suggestive of an organic lesion. However, amyl nitrite caused complete filling and free passage of barium, while colons with proved organic lesions were not modified.

A number of patients showing a definite response to nitrites were given aromatic spirit of ammonia or amyl acetate to inhale. None of these patients had any relief from pain, and there was no modification of the peristalsis. This apparently ruled out the possibility of a psychic reaction to the inhalation of amyl nitrite.

REVIEW OF THE LITERATURE AND COMMENT

Up to the present time few observations on the effect of nitrites on the gastro-intestinal tract have been recorded. The relief from abdominal pain obtained by the administration of nitrites was first reported by Frank [1] in 1875. He found that intestinal cramps caused by lead poisoning were relieved by amyl nitrite. Pal [2] confirmed this action of amyl nitrite, and also showed that gastric crises and angina abdominalis were relieved by amyl nitrite. In 1915 Hirschfelder [3] found that vigorous peristalsis and spasm of the intestines produced by lead poisoning in animals were inhibited by amyl nitrite. In fluoroscopic studies of patients Holmes and Dresser [4] found that amyl nitrite caused cessation of peristalsis and was equal to atropine as an antispasmodic. In the present study there has been found a definite action of nitrites on certain types of abdominal pain, and a very constant action on the motility of the stomach.

The cessation of peristalsis and the diminution in the tone of the stomach and intestines appear to be the only mechanism of the action of nitrites responsible for the relief from pain. Proofs for this action are: (1) cessation of peristalsis or diminution in tone in 95 per cent of all cases studied; (2) complete relief from pain observed in all patients in whom alteration of motility or tone were the only apparent causes of pain; (3) the cessation of peristalsis with diminution of tone and relief from pain simultaneously, observed during the fluoroscopic examination of some of the patients; (4) disappearance of visible peristalsis and pain in patients with pyloric stenosis when nitrites were administered; (5) no effect on the secretory function of the stomach.

In the group of patients with organic lesions, there were twelve who obtained no relief from pain but showed a cessation of peristalsis and diminished tone when nitrites were administered. The difference in the response to nitrite suggests two possibilities: 1. There may be some other cause for the pain than gastric tonicity or motility, since it has been found that whenever motility or tone is the cause of pain, nitrites give relief. 2. The tone of the muscle about the ulcer cannot be modified by nitrites when the lesion involves the muscular coats by direct extension or edema. The latter view is supported to some extent by the manner in

1. Frank, August: Ueber die Veränderungen am Circulationsapparate bei Bleikolik, Deutsches Arch. f. klin. Med. **16**:423, 1875.

2. Pal, J.: Die vasomotorischen Begleiterscheinungen der lanzinierenden Schmerzen und das Alternieren der tabischer Krisen, Wien. med. Wchnschr. **54**:1, 1904.

3. Hirschfelder, Arthur D.: Pathologic Physiology of Lead Colic: Its Relation to Experimental Therapeutics, J. A. M. A. **65**:516 (Aug. 7) 1915.

4. Holmes, G. W., and Dresser, Richard: The Use of Amyl Nitrite as an Anti-Spasmodic, Am. J. Roentgenol. **19**:43 (Jan.) 1928.

which the patients with gastric ulcers responded. The only patients of this group who failed to obtain relief from pain were those with penetrating ulcers. This does not offer an explanation for the failure of response in the other patients, but it suggests the possibility that when an ulcer involves the muscular coats it may not be modified by nitrites.

The action of nitrites on the pain of gastric and duodenal ulcers supports the theory that the pain is dependent on the motility and tone of the stomach rather than directly on the acidity. There is no doubt, however, that the acidity is an important factor in the cause of pain, as has been pointed out by Gonninger,[5] Palmer [6] and others. It is quite possible that in some manner the acidity may control the tone of the stomach.

One other important fact called to attention by this study is the unreliability of using nitrites as a diagnostic means to differentiate angina pectoris from certain upper abdominal conditions that may give rise to precordial or substernal pain, and in those cases of upper abdominal pain in which the question of angina pectoris arises.

The most constant effects of nitrites observed in the fluoroscopic studies were the cessation of peristalsis and the diminution of tone in the stomach and intestines. This action has been a great aid in differentiating deformities of functional origin from those of organic origin. This was especially true in the fluoroscopic examinations made on the colon. The functional spasm of the colon were relaxed, whereas the organic deformities were unmodified.

CONCLUSIONS AND SUMMARY

1. The effect of nitrites on abdominal pain arising from the gastrointestinal tract was observed in sixty patients. All of the patients without organic lesions were relieved by the nitrites, whereas of thirty-three with organic lesions only twenty-one were relieved.

2. Evidence has been offered which indicates that the relief from pain by the nitrites is dependent on the cessation of peristalsis and the diminution in tone. The failure to obtain relief is probably due to the inability of the muscle to relax.

3. Of 200 patients observed in the fluoroscopic studies only 10 failed to show cessation of peristalsis and diminution of tone in the stomach and intestines following the use of nitrites.

4. Nitrites have been found to be a great aid in differentiating organic deformities from functional ones.

5. As an antispasmodic nitrites are to be preferred to atropine, but neither is wholly satisfactory.

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5. Gonninger, M.: Zur Diagnose des Ulcus ventriculi, Berl. klin. Wchnschr. **45**:396, 1908.

6. Palmer, W. L.: Mechanism of Pain in Gastric and Duodenal Ulcer, Arch. Int. Med. **39**:109 (Jan.) 1927.

THE EFFECT OF NITRITES ON THE MOTILITY OF THE GASTRO-INTESTINAL TRACT

II. EXPERIMENTAL STUDY *

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Amyl nitrite has been used extensively in the treatment for angina pectoris and hypertension since its introduction by Lauder Brunton in 1867. Numerous observations, both clinical and experimental, have been made on the action of nitrites on the circulatory system, but very little attention has been directed toward other possible actions of these compounds. The only clinical observations made on the action of the nitrites on the gastro-intestinal tract are those of Reigel and Frank, Pal, and Holmes and Dresser, already referred to in a previous paper.[1] The only experimental work is that of Hirschfelder, who found that nitrites caused cessation of peristalsis in rabbits and cats suffering from experimental lead colic, and who also showed that this action was not vascular in origin but probably a direct action on the intestines.

In a clinical study of the effect of nitrites on the gastro-intestinal tract, it has been found that certain types of abdominal pain were relieved and that the motility of the stomach and intestines was modified by nitrites. The mechanism of this action was not determined from these studies, but several possibilities were suggested: (1) reflex action, (2) vascular action and (3) direct action on the intestines.

The present study was undertaken with the hope of determining the mechanism of this action on the gastro-intestinal tract.

METHODS

Three groups of animal experiments compose this study: (1) fluoroscopic studies of the gastro-intestinal tract, (2) direct observations on the stomach and intestines and (3) observations on the isolated stomach and on intestinal segments.

1. Fluoroscopic studies were made on the gastro-intestinal tracts of dogs and cats. Some of the animals were not anesthetized, while in others barbital sodium (.225 mg. per kilogram of body weight) was employed intraperitoneally or intravenously as the anesthetic. An amount of barium sulphate sufficient to fill the

* Submitted for publication, April 25, 1931.

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1. Beams, A. J.: The Effect of Nitrites on Pain and Motility of the Gastro-Intestinal Tract: I. Clinical Study, Arch. Int. Med., this issue, p. 270.

stomach moderately was given by tube. Nitrites (amyl nitrite, glyceryl trinitrate and sodium nitrite), amyl acetate and pilocarpine were administered during the course of the fluoroscopic examination. The amyl nitrite and amyl acetate were given by placing 8 or 10 drops of the drug on a piece of gauze and holding it over the animal's nose and mouth. Spirits of glyceryl trinitrate (0.05 cc. per kilogram) and sodium nitrite (20 mg. per kilogram) were given intravenously.

The action of the nitrites on the gastro-intestinal tract was also observed after the administration of pilocarpine (1.5 cc. of 2 per cent solution intravenously or subcutaneously).

2. In the second group of experiments, direct observations were made on the stomach and intestines during the administration of nitrites, amyl acetate and pilocarpine. The animals employed in these studies were dogs, cats and rabbits. There were ten animals studied, on which over forty observations were made.

Under barbital anesthesia (intraperitoneal administration) the femoral vein was cannulated, a tracheal cannula inserted, and the abdomen opened in the midline. Sutures were passed through the edges of the abdominal wall and fastened to rods on either side for the purpose of making an extensive exposure of the gastro-intestinal tract. The stomach and intestines were covered with liquid petrolatum.

A careful study was made of the motility of the stomach and intestines, the frequency of the peristaltic waves and the degree of tone before and after the administration of nitrites, amyl acetate and pilocarpine being especially observed. The same technic was followed in the administration of the drug as was described previously, except that amyl acetate and amyl nitrite were inhaled through the tracheal cannula, the possibility of reflex nasopharyngeal irritation thus being eliminated.

3. Kymographic tracings of the rhythmic contractions of isolated intestinal segments of rabbits and of the stomachs of rats were made. The intestinal segments (about 3 cm. in length) were attached to an apparatus for recording the longitudinal contractions, and then placed in a 50 cc. warming chamber containing either a normal Locke's solution or Locke's solution the p_H of which was corrected with sodium hydroxide rather than with sodium bicarbonate. During the early part of these experiments the latter solution was used accidentally, and it was observed that sodium nitrite acted differently than with the normal Locke's solution. For this reason it was employed in all of the experiments. The solutions were aerated and maintained at a temperature of 38 C.

Tracings of the rhythmic contractions of the intestinal segments were recorded on smoked drums before and after the addition of amyl nitrite, sodium nitrite, amyl acetate or sodium chloride in dilutions of from 1 : 50 to 1 : 100,000.

RESULTS

Fluoroscopic Studies.—Cessation of peristalsis and relaxation of the stomach was always observed subsequent to the administration of nitrites, with the exception of amyl nitrite, which infrequently failed to have any effect on the motility. The action of all the nitrites appeared about one-half minute after the administration. With amyl nitrite the effect lasted from three to five minutes, with glyceryl trinitrate from five to ten minutes, and after sodium nitrite from ten to twenty minutes. Amyl acetate had no effect on the motility or tone. This confirms the action already noted in man. The administration of

pilocarpine (subcutaneously) caused vigorous peristalsis in the stomach and intestines. This action occurred in from about two to three minutes after the drug had been given. Nitrites were quite as effective after as before the administration of pilocarpine, although the effects noted were of shorter duration.

Direct Observations on the Stomach and Intestines.—In the experiments in which direct observations were made on the motility of the stomach and intestines, an excellent opportunity was offered to study the action of nitrites more in detail and to obtain fairly accurate measurements of the duration of the action. Amyl nitrite was the only nitrite preparation that failed to produce some response every time it was administered. In one animal amyl nitrite was ineffective; in two others it was ineffective on first administration, although subsequently a definite response was obtained.

About one-half minute after the administration of amyl nitrite, the peristaltic waves of the stomach became shallow and were less frequent, and some of them faded out before reaching the pylorus. At the end of one minute, the waves were entirely absent, and there was relaxation of the stomach. The duration of amyl nitrite was from two to five minutes. In most of the experiments the small and large intestines acted in the same manner as that described for the stomach. In a few instances no action was seen in the intestine, although the stomach responded. The duration of action was the same in both. Inhalation of amyl acetate had no effect on the peristalsis. Glyceryl trinitrate and sodium nitrite had the same effect as that described with amyl nitrite, except that the duration of action was longer and there appeared to be a more definite response. The duration of the action of glyceryl trinitrate was from three to ten minutes, and that of sodium nitrite from five to twenty minutes.

After the administration of pilocarpine, vigorous peristaltic waves were seen in the stomach and intestines. The waves were very deep, and from six to eight contractions per minute were observed in the stomach. The nitrites continued to have the same inhibitive effect on the motility of the stomach and intestines as they had before the administration of pilocarpine. The duration of the action was shorter, and at times, with the administration of amyl nitrite, the only change noted was a slowing and very shallow peristaltic waves that failed to reach the pylorus. However, with glyceryl trinitrate and sodium nitrite the action was striking. One minute after the administration of the glyceryl trinitrate or sodium nitrite, the vigorous peristalsis and hypertonicity of the gastro-intestinal tract were replaced by relaxation and inactivity.

Observations on the Isolated Stomach and Intestines.—With amyl nitrite a very constant effect was seen in all of the experiments. Immediately following the introduction of the drug into the chamber of Locke's

solution there was a sudden diminution in the tone and cessation of the rhythmic contractions (fig. 1). This lasted from one to three minutes. Then there was a gradual improvement in the tone, amplitude and frequency with complete recovery at the end of from four to ten minutes. There appeared to be a definite relation between the duration of the action and the amount of drug introduced.

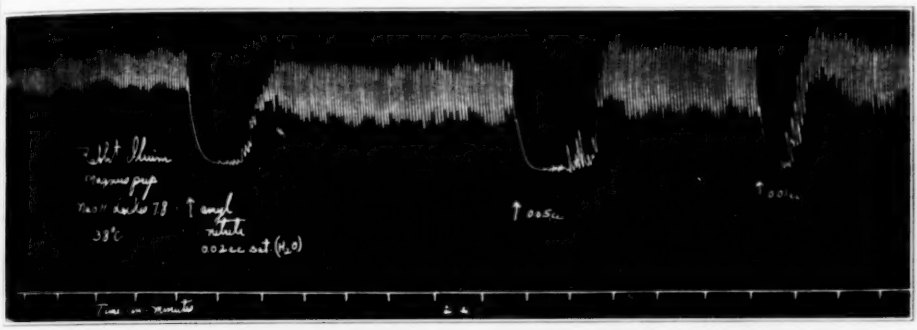

Fig. 1.—Tracing of an intestinal segment showing the effect of amyl nitrite. Immediately following the introduction of the drug, there was a fall in tone and a cessation of rhythmic contractions.

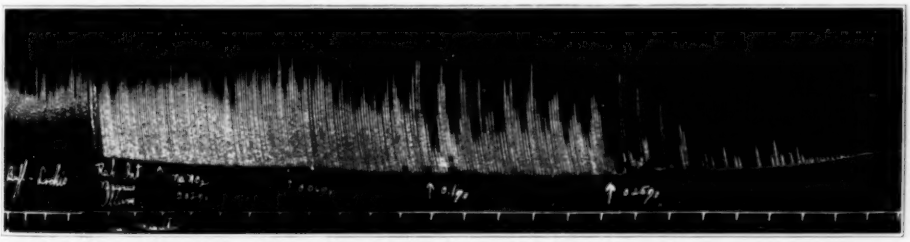

Fig. 2.—Tracing of an intestinal segment immersed in Locke's solution. No change was seen in the rhythmic contractions until after a total of 0.5 cc. of a 10 per cent solution of sodium nitrite had been introduced. The contractions were then irregular, with a decrease in amplitude until they ceased entirely.

Sodium nitrite did not cause as constant or prompt an action as amyl nitrite. In the experiments in which the normal Locke's solution was employed, the effect most frequently observed was a gradual decrease in the amplitude and frequency of the contraction over a period of ten or fifteen minutes, when contractions entirely ceased (fig. 2). Recovery was uncommon.

The action of sodium nitrite was more constant in the Locke's solution p_H corrected by sodium hydroxide than in normal Locke's solution. Immediately following the introduction of sodium nitrite there was a definite increase in tone with a marked diminution in amplitude and frequency of contractions (fig. 3). The rise in tone was of short duration (lasting from one-half to one minute), and was followed by a gradual fall, so that the terminal level was far below its original level. With the fall in tone, a temporary improvement in the amplitude and frequency occurred, but as the tone decreased, the amplitude and frequency became less until often the contractions entirely disappeared. In many cases recovery did not occur, but as a rule recovery was observed. In those

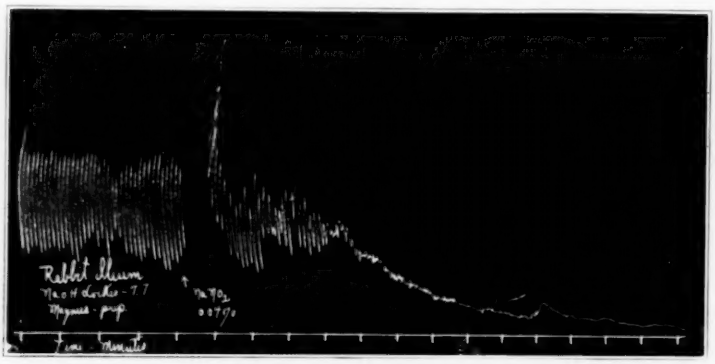

Fig. 3.—Tracing of an intestinal segment immersed in Locke's solution, the p_H of which was corrected by sodium hydroxide. The arrow indicates the introduction of 0.2 cc. of a 10 per cent solution of sodium nitrite (0.04 per cent). There was first a rise and then a fall in the tone, with a gradual diminution in the amplitude of the contractions.

segments in which partial recovery occurred, the contractions were arrhythmic, the rate was diminished and the contractions irregular. The tone usually remained below the original level.

Exceptionally, segments immersed in normal Locke's solution reacted in a manner quite similar to that of segments immersed in Locke's solution corrected by sodium hydroxide. As a rule, failure to respond to sodium nitrite was more frequent in the presence of normal (buffered) Locke's solution than in the Locke's solution of the same p_H corrected by sodium hydroxide.

Amyl acetate or sodium chloride had no effect on the intestinal segments even in much greater concentrations than that employed in amyl nitrite or sodium nitrite.

COMMENT

The fluoroscopic examinations and the direct observations made on the gastro-intestinal tracts of the animals studied offered very little information as to the mechanism of the action of nitrites.

In the studies made on the intestinal segments, the nitrites caused a definite change in the rhythmic contractions and tone. This action of nitrites rules out the possibility of a reflex or vascular action, and places the site of action in the intestines. It is impossible to state whether or not it acts entirely on the muscle with the evidence that is offered.

The failure of amyl acetate to produce any effect on the intestinal segments rules out the amyl ion as a possible cause of the actions of amyl nitrite observed. Sodium chloride had no effect on the rhythmic contractions. It is quite probable therefore that neither the sodium ion or alterations of isotonic conditions are of significance in explaining the sodium nitrite reaction. The initial rise seen after the introduction of sodium nitrite in the Locke's solution with the p_H corrected by sodium hydroxide is not due to hypertonicity of the nitrite dosage that was added to the bath. No explanation of this reaction is offered, nor is there an explanation for the number of failures in the response in normal Locke's solution compared with Locke's solution buffered by sodium hydroxide.

TRANSIENT VENTRICULAR FIBRILLATION

A STUDY OF THE ELECTROCARDIOGRAMS OBTAINED FROM A PATIENT WITH AURICULOVENTRICULAR DISSOCIATION AND RECURRENT SYNCOPAL ATTACKS*

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It is now definitely established from recorded observations that transient syncopal attacks occurring in patients with permanent auriculoventricular dissociation are due in the main to one of two conditions; either to complete standstill of the ventricles or to the various grades of acceleration leading to ventricular fibrillation. The former mechanism, which is the more common, has been excellently reproduced in the dog, in which heart block had been established,[1] and from correlations with the clinical and graphic manifestations observed in man there is now a fairly accurate knowledge of some of the successive events leading to and following transient ventricular standstill.

Comparable analyses of the disturbances leading to the onset and recovery from transient ventricular fibrillation in the presence of auriculoventricular dissociation are lacking, for spontaneous recovery from ventricular fibrillation in the larger intact animal is unknown if the rhythm is induced by any of the methods now available.[2] Consequently, for the present at least, knowledge of the mechanism responsible for syncopal attacks in which ventricular acceleration instead of ventricular standstill takes place will have to come from careful observations on human beings subject to such seizures.

I am reporting observations on a patient who suffered sixty-seven seizures of unconsciousness during a period of seven months while she was at the Montefiore Hospital. The duration of these syncopal attacks varied from a little over one minute to the longest recorded seizure which lasted six minutes and two seconds and was followed by recovery. Electrocardiograms were obtained of all or of part of twelve such

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2. Wiggers, C. J.: Studies of Ventricular Fibrillation Caused by Electric Shock: I. The Revival of the Heart from Ventricular Fibrillation by Successive Use of Potassium and Calcium Salts, Am. J. Physiol. **92**:223, 1930.

seizures accompanied by syncope, and in each instance the underlying mechanism proved to be ventricular fibrillation.

From numerous other electrocardiograms taken of this patient preceding, during and subsequent to her syncopal attacks, it has been possible to draw a fairly accurate picture of the successive alterations that took place in her heart rate and rhythm preceding and succeeding ventricular fibrillation.

REPORT OF A CASE

History.—G. S., a woman, aged 66 and weighing 112 pounds (50.8 Kg.), was admitted to the Montefiore Hospital on July 16, 1929, and died on Feb. 5, 1930. Her chief complaints on admission were progressive shortness of breath, weakness and recurrent attacks of loss of consciousness. Her symptoms were of one year's duration.

In January, 1928, the patient was informed for the first time that she had high blood pressure. She had been in good health up to that time. One day in February she suddenly dropped to the floor and became unconscious. It was observed by members of her family that during such seizures of unconsciousness, she showed twitchings of the face and upper extremities, with rolling of her eyes and profound stertorous breathing. Between February, 1928, and April, 1929, she experienced eight such seizures. Between these attacks she felt perfectly well, except for slight headaches, which were more pronounced in the morning. Since the middle of April, 1929, the attacks of unconsciousness had become more frequent, numbering at times several in one day.

In addition to these major and severer attacks, she also complained of briefer periods of giddiness and fainting sensations sometimes lasting only a few seconds and frequently accompanied by a consciousness of "palpitation" of the heart. She had had over thirty such spells during one day almost five weeks prior to her admission to the Montefiore Hospital, but since that time she had not had any major attacks of unconsciousness.

Examination.—Examination on admission to the Montefiore Hospital revealed an elderly Jewish woman, slightly dyspneic, mentally clear and quite intelligent. Her lips were cyanotic, but her face and skin had a lemon yellow tint. All of her teeth were missing, which probably accounted for the fact that her tongue showed no signs of having been bitten during any of the periods of unconsciousness. Her pupils were equal, and both reacted to light and in accommodation. The right carotid artery was thickened, and near the lateral border of the sternomastoid muscle it was very stiff and tortuous. The superficial jugular veins were markedly distended, and 2 and sometimes 3 auricular beats could be seen pulsating to each ventricular contraction of the heart. The apical impulse of the heart was in the sixth intercostal space in the anterior axillary line. The heart sounds were of poor quality, the first sound at the apex being very weak. Occasionally it would be loud, and at such times it was noted that the ventricular contraction occurred simultaneously with that of the auricle. The aortic second sound was markedly accentuated.

The pulses were slow, slightly irregular but of good force. The ventricular rate was approximately 38 beats per minute when counted over a period of several minutes. In the interventricular silences, 2 and sometimes 3 auricular sounds could be heard distinctly near the third intercostal space to the left of the sternum. The radial arteries were thickened and in parts beaded. The blood pressure was 280 mm. of mercury systolic and 80 mm. diastolic when the ventricular rate averaged 38 beats per minute.

Over the lungs posteriorly only a few moist râles could be heard. The abdomen was soft and lax, and the edge of the liver was palpable 6 cm. below the costal margin in the midclavicular line.

Roentgen examination of the chest did not reveal any abnormalities in the lungs. On fluoroscopic examination the pulsations of the left auricle could be seen independent of the ventricular contractions at the rate of about three and four auricular contractions to one ventricular contraction. The left ventricle was concentrically enlarged and had a high take-off. The aorta was wide and elongated and showed in its arch several calcific plaques.

An electrocardiogram taken on the day of admission revealed left ventricular predominance and complete auriculoventricular dissociation. The ventricular complexes were all of the supraventricular form. The basic ventricular rate varied from 17.7 beats per minute to 24.1 beats, and the auricular rate was 100 beats per minute. The T waves were markedly negative in all three leads. At times there was definite bigeminal rhythm, owing to premature ventricular beats.

Course.—Although the patient had been free from symptoms for the preceding five weeks, one day after her admission to the Montefiore Hospital she began to complain of short recurrent spells of dizziness. At 4:30 p. m. on July 17, 1929, she was seen at the hospital in her first major syncopal seizure.

Preceding this attack she was standing, and her heart rhythm was found to be irregular, there being at times definite bigeminal rhythm. The basic ventricular rate averaged 40 beats per minute, not including the premature ventricular contractions. Infrequently, I could feel the pulse suddenly collapse for a few seconds, so that no beats were palpable at the wrist. During these short periods the patient's face would become pale, she would shut her eyes, shake her head a bit with a few twists of the shoulders and then open her eyes again and sigh very deeply when it was over. After a few such minor seizures, the patient became suddenly motionless and dropped into an arm chair. Her eyes became fixed; her face assumed an expressionless attitude and became almost deathly pale, and there was intense cyanosis of the lips. She suddenly stretched out her hands and legs stiffly, and her head turned involuntarily toward the left side and toward the back. Her eyes began to roll slowly and irregularly to the left and upward. She began to breathe stertorously with her mouth at first open and then shut tightly, using all of her accessory inspiratory muscles. She foamed at the mouth. A sudden convulsive seizure was followed by an intense flush of the face and neck which coincided with a barely perceptible slow pulse of about 45 beats per minute at first. This lasted only a few seconds, and was followed by a rapid pulse rate of about 100 beats per minute. The pulse rate slowed within four seconds to almost 40 beats again. With the onset of the rapid pulse rate, irregular auricular pulsations were again visible in the neck veins. As the patient regained her normal color she began to breathe more freely, and she asked for a drink of water.

This whole period of syncope lasted about two minutes, during which time no auricular pulsations were visible in the neck veins, nor was there any palpable pulse at the wrist.

The patient was seen again in another syncopal attack on July 22, at 12:10 p. m. At this time the pulse rate seven minutes prior to the seizure was 40 beats per minute and irregular. The auricular rate as counted from the pulsations of the veins in the neck was about 95 beats per minute. During this attack, which lasted exactly one minute and twenty seconds, clinical observations were carried out with only one point in view, and that was to study the auricular rate and rhythm, which was made possible by the markedly distended deep veins of the neck. Her pulse rate was counted at the same time.

During this seizure no auricular pulsations were visible, nor was there any palpable pulse at the wrist, and the heart sounds were totally absent. At the end of this attack, which was somewhat similar to the preceding one, faintly visible but rather frequent and irregular beats were seen in the neck veins. At first these averaged one to each beat felt at the pulse, then they increased in frequency to about 60 beats per minute within the next thirty seconds, and subsequently to 120 beats to the minute for the ensuing 50 seconds. The pulse rate was almost equal to the auricular rate, although it was slightly irregular and variable. Within two minutes after the cessation of the attack, there was definite coupling at the wrist, with the rate at 62 beats per minute. In another minute the pulse rate slowed to 44 beats per minute, and the auricular rate, which was now regular, averaged 100 beats.

Within the next five weeks of the patient's stay in the hospital, she was ambulatory and free from all symptoms. During this period she received 30 minims (1.84 cc.) of saturated solution of potassium iodide daily. At first the frequency of the attacks in the ensuing weeks was attributed to the effects of the drug, but the seizures became even more frequent when the drug was omitted.

A total of sixty-seven syncopal attacks with epileptiform seizures were noted between the day of her admission to the hospital and the day of her death, when she was seen in her last attack, which lasted almost thirteen minutes but consisted of several rapid recurrent seizures of transient ventricular fibrillation, one following the other in rapid succession, with alternate restoration of the basic and dominant ventricular rate and rhythm.

ALTERATIONS IN THE ELECTROCARDIOGRAM PRECEDING VENTRICULAR FIBRILLATION

Prolonged observations on the patient whose case has been reported, following the first recorded attack and its premonitory period, have amply demonstrated the possibility of recognizing in her clinically the onset and appearance of transient ventricular fibrillation in practically the order revealed by the electrocardiograms.

Although the records of the several syncopal attacks differed slightly at both the onset and offset, depending in part on the duration of the seizures, the stages preceding the onsets of ventricular fibrillation were fairly constant and uniform, judging from the electrocardiograms obtained. It is probable that similar seizures in other patients with complete auriculoventricular dissociation and transient ventricular fibrillation are preceded by like events, differing only in the premonitory period, which may last, as in this patient, only a few hours at one time and several days at another.

The average basic ventricular rate oscillated between 28 and 36.5 beats per minute (fig. 1). The lowest regular ventricular rate recorded was 17.5 beats per minute at a time when the patient was up and about. The Q-R-S complexes were all of the supraventricular form, but were followed by an unusually large, wide and completely inverted T wave. Infrequently, the Q-R-S complexes were variable from beat to beat

in height as well as in duration, often assuming transitional changes from a dextrocardiogram to a levocardiogram and vice versa.

In the intervals between the syncopal attacks, the basic ventricular rate was regular, and was not influenced by exercise or by sleep during the day. It was not affected by the subcutaneous administration of atropine sulphate in doses of 1/50 of a grain (0.0019 Gm.) or by pressure over either carotid artery or on the eyeballs.

A ventricular rate of 36 beats per minute could be increased temporarily, but only for a few minutes, to 41 beats, at a time when no

Fig. 1.—Left ventricular preponderance. Complete auriculoventricular dissociation. The ventricular complexes were all of the supraventricular form. The T waves were negative in all three leads. The basic auricular rate was 93.7. The basic ventricular rate was 36.5.

extrasystoles were present, by the subcutaneous injection of 0.5 cc. of a 1 : 1,000 solution of epinephrine. No premature beats of the ventricles could be elicited in this way.

During the presence of a regular ventricular rate, the auricles also beat regularly, but their rhythm was independent of that of the ventricles. At times a slight irregularity was present because of shortening of the interauricular periods during the presence of a ventricular contraction. The auricular rate was easily accelerated temporarily by exercise and the subcutaneous administration of atropine sulphate in

doses of 1/100 grain (0.006 Gm.) subcutaneously. However, repeated pressure over the right carotid artery did not influence their rate or rhythm.

On several occasions when tracings and heart counts were made on the patient repeatedly throughout the day, the basic ventricular rate preceding the onset of ventricular fibrillation behaved somewhat similarly to that observed by me previously in a patient with complete auriculoventricular dissociation who had been deeply under the influence of toxic doses of digitalis.[3]

At first there was a gradual increase in the basic ventricular rate from an average of 28 beats during the presence of auriculoventricular dissociation to a ventricular rate of 42.8 beats, with the appearance of a partial heart block and a regular auricular rate of 83.3 beats, two auricular contractions being followed by one ventricular systole (fig. 2). After a few hours of this rhythm, which remained uninfluenced by effective doses of atropine or by carotid sinus pressure, there was a spontaneous increase in the rate of the auricles to 103.4 beats and the reestablishment of complete auriculoventricular dissociation with a 5:2 sequence (fig. 3 *A-E*).

Clinically, this rhythm resembled somewhat that of a bigeminy, but the electrocardiograms revealed this irregularity to be due to an adaptation of certain auricular contractions to that of the ventricles, producing alternately prolonged and shortened interventricular periods depending on the simultaneous contractions of each third auricular beat to that of the ventricles.

In the electrocardiograms, the Q-R-S deflections appearing at the time of a superimposed contraction invariably assumed the form of a dextrocardiogram (fig. 3 *A, C*). This was not merely a fortuitous observation, since it was encountered on more than one occasion when records were taken over a long period of time.[4]

This condition, simulating a bigeminal rhythm clinically, after persisting for a little over one hour at one time and several hours at another was suddenly transformed into a 2:1 heart block, with an increase of the ventricular rate to 46.8 beats per minute and an auricular rate of 93.7 beats, whereas previously the auricles had a rate of 103.4 beats (fig. 3 *E-F*).

A further increase in the dominant ventricular rate to 50 beats before the onset of ventricular fibrillation at one time was accompanied by similar transitions, as has been described, only at a higher rate of both the auricles and ventricles.

3. Schwartz, S. P.: The Action of Digitalis in Complete Heart Block: Its Toxic Influence on the Idio-Ventricular Rate and Rhythm, Am. Heart J. **4**:408, 1929.

4. All these studies were carried out on lead 2 only.

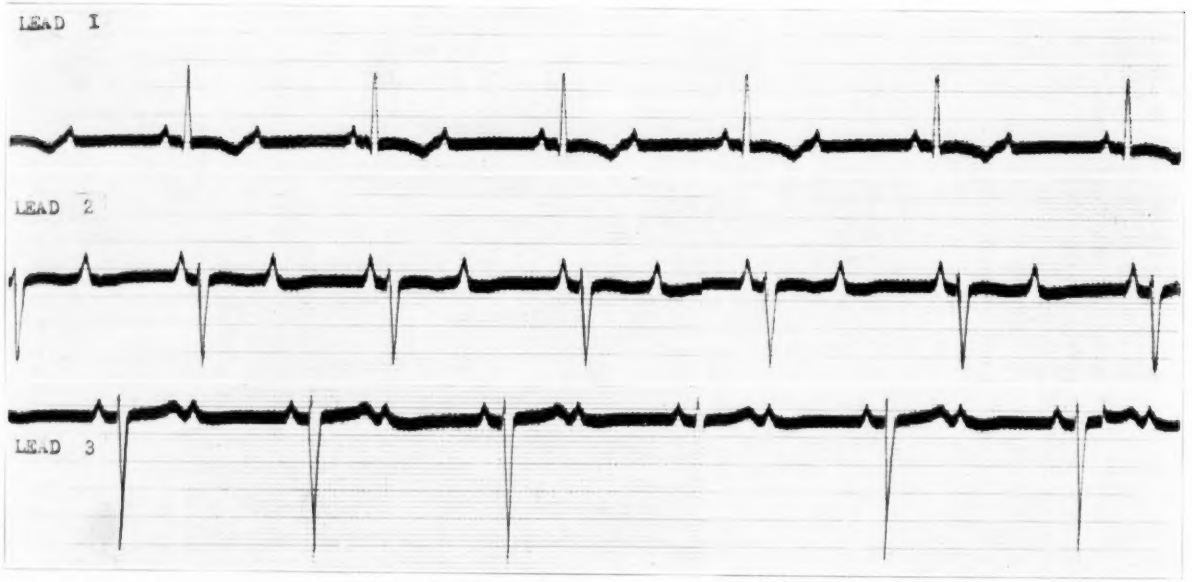

Fig. 2.—Apparent partial heart block with a regular ventricular rate of 42.8 beats and an auricular rate of 83.3. The main ventricular deflection was downward in lead 2, as compared with the previous record.

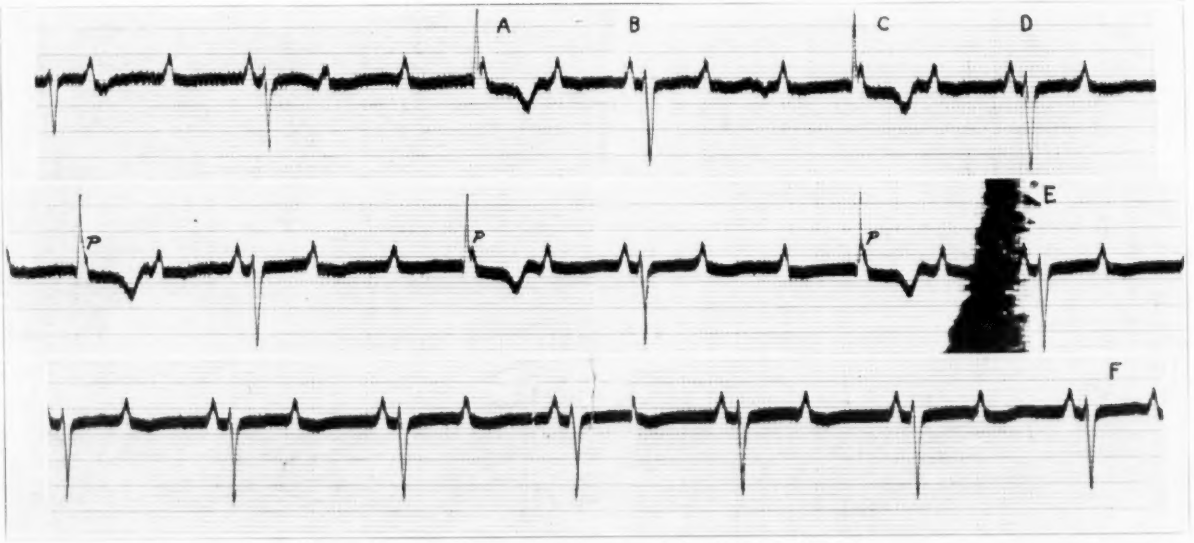

Fig. 3.—Continuous strip; lead 2 only. This record was obtained twenty minutes after the preceding one. At first, the auricular rate was inconstant and averaged 103.4 beats per minute. The ventricular rate was also inconstant, there being a 5:2 block between *A* and *E*. A bigeminal rhythm was produced by the simultaneous contraction of each third auricular beat with that of the ventricles. At such times the main ventricular complex was upward instead of downward. At *E* there was a change from a 5:2 block to a 2:1 block, with a concomitant reduction in the auricular rate of 93.7.

On several occasions, it was possible to register seizures of paroxysmal ventricular fibrillation coming in rapid succession at intervals of from one-half to one minute, the patient alternately regaining consciousness with the restoration of the basic ventricular rhythm. At such times the ventricular rate, when recorded between the attacks and pre-

Fig. 4.—Continuous strip; lead 2 only. *A*, the end of a seizure of transient ventricular fibrillation; *B*, the postundulatory pause; *C*, the onset of the intermediary idioventricular rhythm; *F*, the establishment of the basic ventricular rhythm; *G*, a premature beat initiating the tachysystolic stage (*G-I*) preceding another seizure of transient ventricular fibrillation.

ceding a period of syncope, averaged 50 and 62.5 beats, respectively, per minute, and was almost regular for long periods at a time (fig. 4 *F-G*).

In short, a paroxysm of ventricular fibrillation was always preceded by a gradual acceleration through steplike progressions of both the basic auricular and ventricular rate, the highest regular ventricular rate recorded being 65.2 beats per minute.

In addition to these increasing variations in the rate of the dominant auricular and ventricular rhythm, premature beats of a distinct type and appearing at first alternately, so as to form a bigeminal rhythm, began to disturb the regularity of the heart. The electrocardiograms reveal that these extrasystoles invariably and uniformly arose from the same focus (fig. 4 *G* and fig. 5 *B, D*). Both the Q-R-S complexes as well as the T waves are distinctly different in size, shape and form from those of the dominant ventricular beats.

When the main complexes of the basic ventricular rhythm are dextrograms instead of levograms, these initial alternate extrasystoles assume a slightly different form, but they are of the same character when the phenomenon is repeated, their voltage and duration being almost the same, the intervals measuring slightly less or more than twelve hundredths of a second (fig. 6 *B, C, D, E*).

The electrical deflections that follow these alternate extra beats, so as to increase further the ventricular rate and disturb the regular rhythm, are very variable from time to time.

The onset of their appearance is also variable. Frequently, only two extra beats are added to the bigeminy, and this sequence of events is repeated as such or is occasionally interrupted by a trigeminal or polygeminal rhythm coming at almost regular intervals after 2, 3 or 4 regular auricular beats precede it (fig. 5 *B-C* and fig. 6 *E-F*).

Infrequently, groups of from 5 to 10 beats would disrupt this rhythm, each extra beat so superimposed on the other as to distort the contour of the main ventricular deflection (fig. 5 *D-E* and fig. 6 *B*). The auricular sequence does not appear to be disturbed during these short runs of superimposed ventricular beats. Clinically, at such times, the patient was never observed to have lost complete consciousness.

While such short runs of from 5 to 10 beats were observed to disturb the rate and rhythm for hours at a time, ventricular fibrillation with definite syncope was not ushered in unless the basic ventricular rate as well as the auricular rate had definitely increased independent of the presence of premature beats.

ALTERATIONS IN THE ELECTROCARDIOGRAM DURING VENTRICULAR FIBRILLATION

The onset of every recorded seizure of ventricular fibrillation in the patient was initiated (comparisons are made of lead 2 only) by a ventricular extrasystole that was always of the same character and appar-

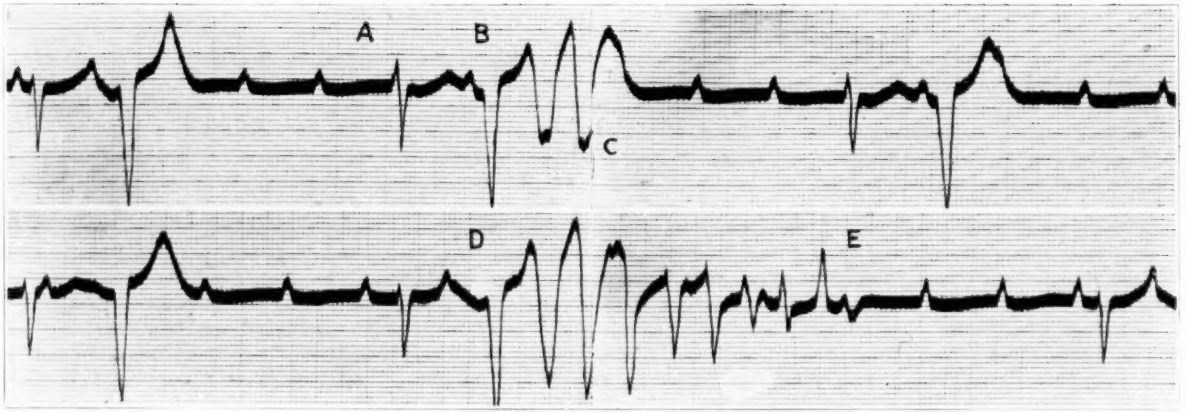

Fig. 5.—Continuous strip; lead 2 only. The main ventricular deflection is a levocardiogram; periods of reexcitation consisting of a succession of ventricular beats, superimposed on each other so as to increase the ventricular rate of 300 beats per minute. Note that the initial ventricular deflection initiating these short runs is always of the same shape, size and form.

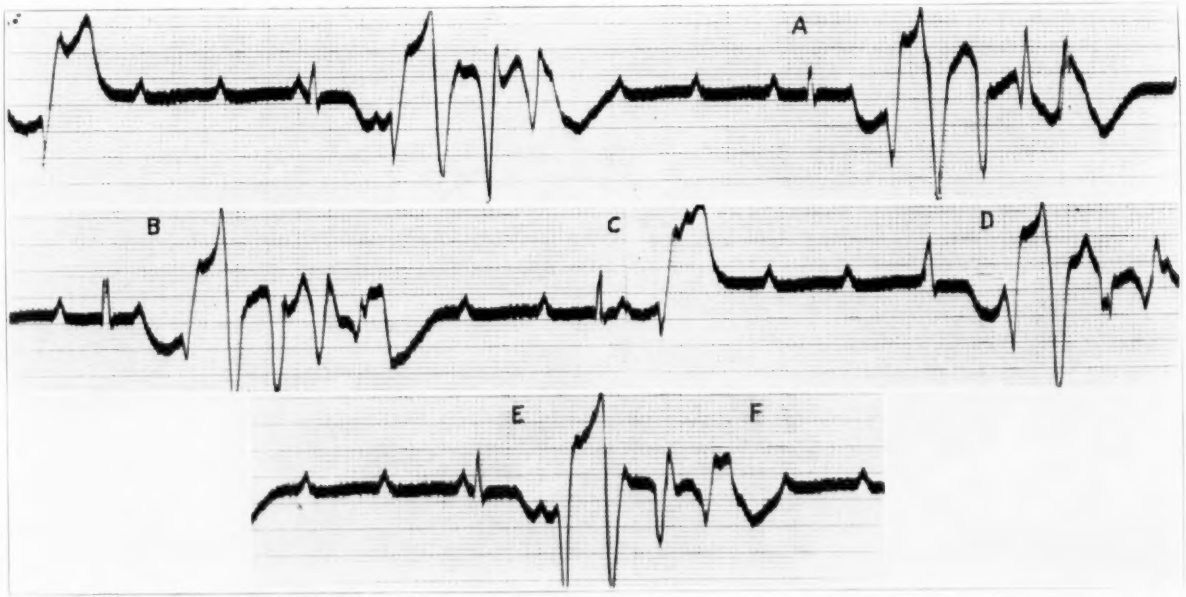

Fig. 6.—Continuous strip; lead 2 only. The main ventricular deflection is a dextrocardiogram. Recurrent groups of ventricular beats interrupted a slow basic ventricular rate. Note that the premature beat initiating each group is always of the same shape and form. The auricular rate of 115.3 beats was regular and not disturbed by the periods of ventricular reexcitation. The patient complained of dizziness and spots before the eyes at such times.

ently arose from the same focus in the ventricle. This deflection, measuring 0.12 second and accompanied by an unusually large T wave, was followed by a series of Q-R-S complexes, one superimposed on the other, which for 2 or 3 beats at the most were of large size (fig. 4 *G*). Sometimes this extrasystole would be followed for several beats by complexes similar in form to it but smaller in amplitude. A sudden increase in the ventricular rate to approximately 120 beats would then continue for eight or ten seconds before the appearance of smaller, more regular and faster oscillations. This "tachysystolic" stage immediately preceding ventricular fibrillation was due to a ventricular arrhythmia with deflections that appeared to arise from multiple foci of the ventricles.

On one occasion a period of unconsciousness with epileptiform seizures lasting over four minutes was initiated by an irregular ventricular tachycardia with a rate of 125 beats per minute, lasting for 26.2 seconds before ventricular fibrillation set in. The ventricular complexes of this "tachysystolic" stage, although lower in amplitude, resembled very closely the usual initial ventricular extrasystoles associated with the onset of ventricular tachysystole or fibrillation (fig. 8 *B-C*).

During a typical major period of syncope accompanied by epileptiform seizures, the rate of the ventricular oscillations varied from a minimum of 250 beats per minute to a maximum of 1,000 beats. The oscillations during this period differed from each other in amplitude and duration and there was a periodic waxing and waning of the electrical deflections, some of the waves being greater in voltage than those of the basic ventricular deflections (fig. 7).

This phasic variation in the deflections of the electrocardiograms persisted until the end of the syncopal attacks.

A few seconds before ventricular fibrillation ceased, however, the oscillations increased in amplitude, reaching at times a voltage of 30 mm., the deflections became wider and more irregular, some being 0.4 second in duration; they were distinctly separated from each other by a short interval, and then an abrupt change in the mechanism followed (fig. 9, lead 1 and fig. 10 *B*).

MODE OF RECOVERY FROM VENTRICULAR FIBRILLATION

Two distinct modes of recovery from ventricular fibrillation were observed. In one type, the fibrillation ceased promptly and was followed by a postundulatory pause varying from 0.8 second to 1 second (fig. 4 *B*). The basic ventricular rhythm did not appear, however, for several seconds after this and it was preceded by an idioventricular rhythm, with a slightly irregular rate averaging 60 beats per minute.

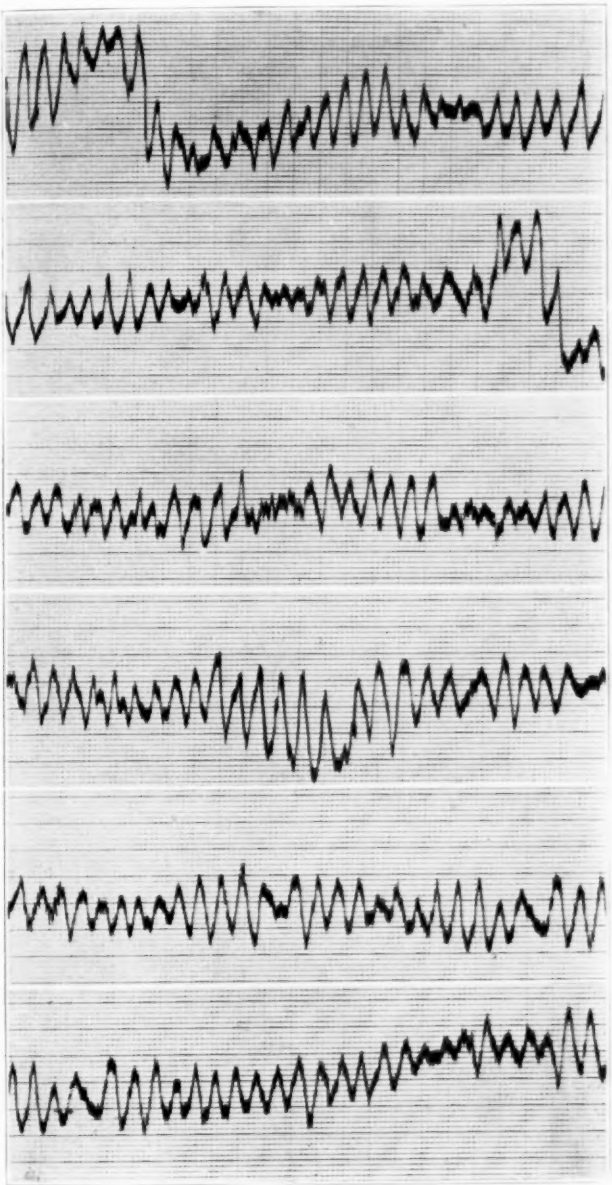

Fig. 7.—Continuous strip; lead 2 only. Record obtained during a period of unconsciousness. The ventricular rate varied from 300 to 1,000 beats per minute. There was periodic waxing and waning of the atypical ventricular complexes.

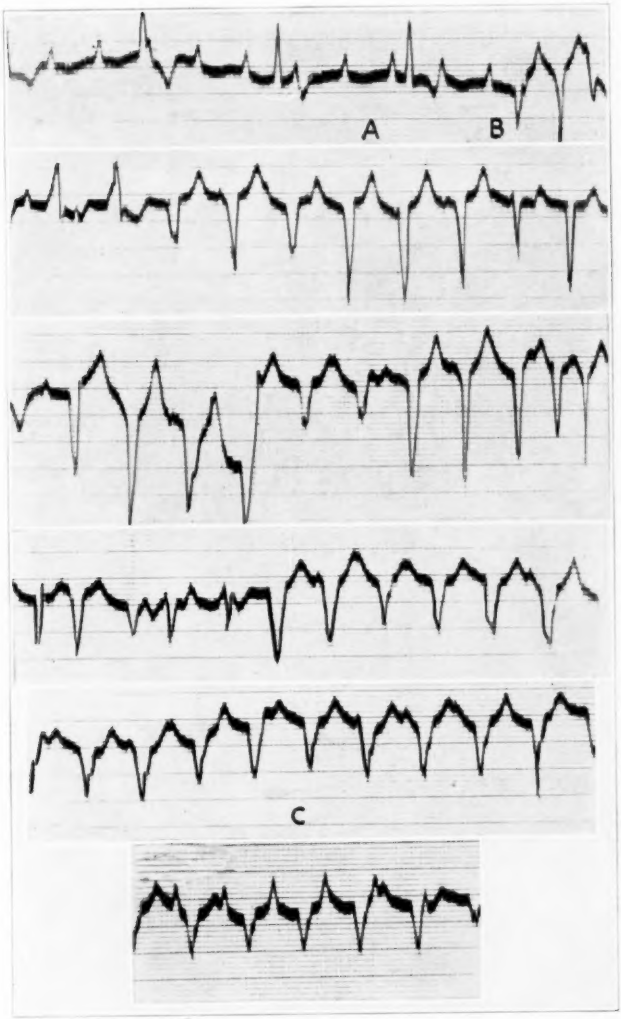

Fig. 8.—Continuous strip; lead 2 only. A period of tachysystole with a slightly irregular ventricular rate of 150 beats per minute followed a basic ventricular rate of 65.2 beats and preceded a transient seizure of ventricular fibrillation. The auricular rate kept pace with the ventricular in this stage.

Although the initial beat of this idioventricular rhythm was occasionally different (fig. 4 *C*), the complexes forming this rhythm were usually all of the same form. They were wide deflections with abnormally large T waves, some of which increased progressively in size (fig. 4 *D-E*).

The second type of recovery was also sudden, but was not followed by a postundulatory pause. A careful study of such a record of recovery reveals an idioventricular beat initiating an idioventricular rhythm with ventricular complexes totally different from those of the

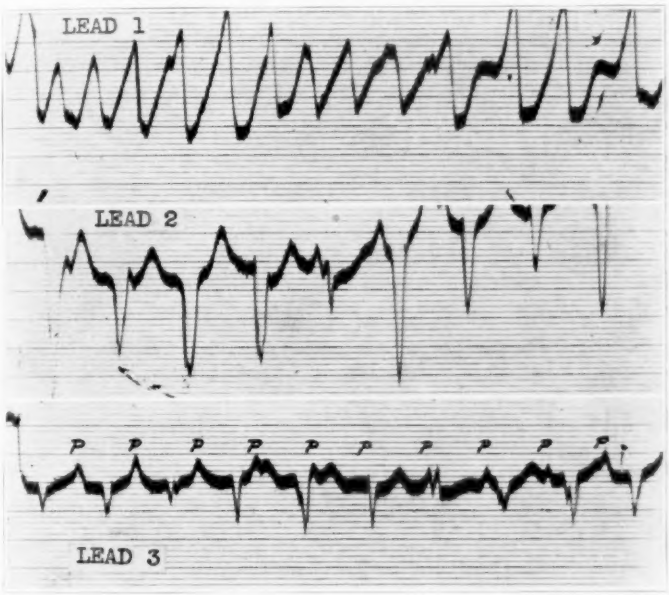

Fig. 9.—Three leads taken in rapid succession. The end of a period of transient ventricular fibrillation, best seen in lead 1, was followed by a tachysystole of 160 beats per minute prior to revival of the normal mechanism.

dominant and basic rhythm (fig. 10 *B*). A postundulatory pause is not visible since an idioventricular beat is seen to arise from the last of the waves terminating the ventricular fibrillation.

As in the previous type of recovery, this rhythm, averaging about 60 beats per minute, lasted only from nine to twelve seconds before the appearance of the basic ventricular rate, which was always high (60 to 90 beats per minute) even in the presence of complete auriculo-ventricular dissociation. The onset of the dominant rhythm seems to have some definite relationship to the appearance of auricular con-

tractions (fig. 4 *E-F*). Complete restoration of the usual rhythm following ventricular fibrillation was observed to come after three successive auricular contractions appeared subsequent to an idioventricular beat.

On one occasion transition from ventricular fibrillation to the basic rhythm was gradual, and it was interrupted by a tachysystolic stage with a ventricular rate of 120 beats per minute, the ventricular complexes of

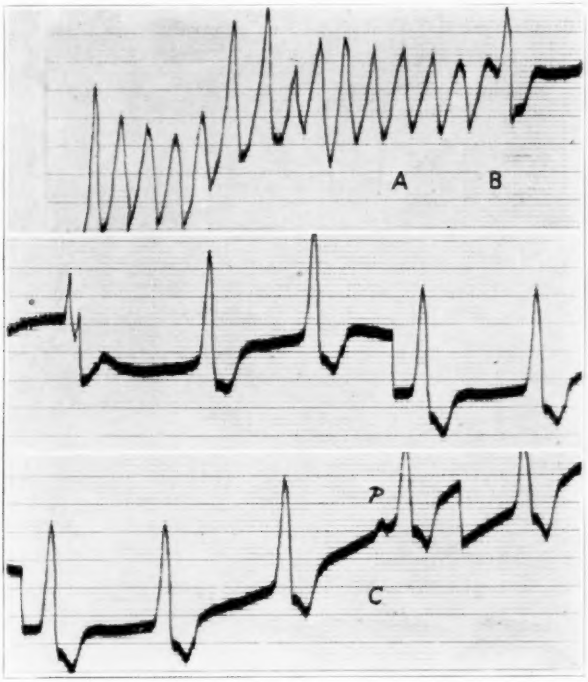

Fig. 10.—Continuous strip; lead 2 only. Record obtained at the end of a period of unconsciousness which coincided with cessation of a seizure of transient ventricular fibrillation. The intermediary idioventricular rhythm preceding the development of the basic ventricular rate may be seen between *B* and *C*.

which varied in size, shape or form from beat to beat. The auricular rate during this period of recovery kept pace with the ventricular rate, and restoration to the basic rhythm took place as in the previous recoveries, the dominant beat appearing after three successive auricular beats (fig. 9, leads 1, 2 and 3).

When clinical and graphic correlations were made, the return to consciousness coincided with the termination of the ventricular fibrilla-

tion and the appearance of either the idioventricular rhythm or the post-fibrillation period of tachysystole.

COMMENT

These observations reveal that syncopal seizures in patients with auriculoventricular dissociation may result from ventricular fibrillation. A few such cases are recorded in the literature.[5] It is of particular interest to note that the mechanism responsible for the syncopal attacks in this case was always of the same nature when recorded, namely, ventricular acceleration instead of ventricular standstill, which has been observed in others. It is most likely that the other unrecorded seizures observed in this patient were also of the same nature and not due to ventricular standstill, for the premonitory periods and periods of recovery noted clinically resembled each other very closely and were similar to those recorded. In this instance every syncopal seizure, whether recorded graphically or studied clinically, was preceded by a definite progressive increase in the basic ventricular rate from an average of 38 beats per minute to as high as 65.2 beats. Consequently, the erroneous impression gained from some studies [6] that syncopal seizures never occur in patients with auriculoventricular dissociation if the established ventricular rate is greater than 25 beats per minute should be discarded.

It is very likely that this gradual increase in the regular ventricular rate with steplike progressions is a necessary precursor in the mechanism responsible for the development of ventricular fibrillation in this patient.

There is experimental evidence that the ventricles are able to assume a higher rate of rhythm more readily if this rate is approached gradually than if it is approached abruptly. It has been shown by Mines [7] that with increasing frequency of stimulation, each wave of excitation in the heart muscle is propagated more slowly, but lasts a shorter time at any one point in the muscle. The wave of excitation becomes slower and shorter. Similarly, the refractory phase is shortened. It follows that by gradual acceleration, the ventricles can be caused to beat at a higher rate than if the rate of stimulation is abruptly raised.

While the experimental evidence for this phenomenon is based on the increase in the ventricular rate during the presence of sinus rhythm, I have also observed it in a patient with complete auriculoventricular dissociation following the administration of toxic doses of digitalis.[8]

5. Davis, D., and Sprague, H. B.: Ventricular Fibrillation: Its Relation to Heart Block, Am. Heart J. **4**:559 (June) 1929.

6. Read, J. M.: Complete Heart Block: Roentgen-Kymographic Study, Arch. Int. Med. **45**:59 (Jan.) 1930.

7. Mines, G. R.: On Dynamic Equilibrium in the Heart, J. Physiol. **46**:34, 1913.

In a woman with complete heart block and a basic ventricular rate of 37.3 beats per minute, the sequence of events after the use of digitalis in more than the "average therapeutic dose" was almost exactly the same as the premonitory period observed in the patient whose case is herewith reported when this period was studied prior to the onset of a seizure of transient ventricular fibrillation.

At first, there was an increase in the ventricular rate from 37.3 beats per minute to 48.4 beats. From then on the increase in the idioventricular rate was progressive, until it reached 65.2 beats per minute, independent of the presence of any premature beats. On several occasions in this period of gradual acceleration, the electrocardiograms revealed abrupt changes from a complete auriculoventricular dissociation to what appeared as 2:1 partial heart block, and this was invariably accompanied by a transition of the Q-R-S complexes from a dextrocardiogram to a levocardiogram and vice versa, as the ventricular rate progressively increased. In the meantime, at a point where the basic ventricular rate averaged 53.5 beats, extrasystoles of an unusual type, with high voltage and wide deflections, began to interrupt the regular basic rhythm. At first these appeared alternately so as to form a bigeminal rhythm, but as the drug became more effective and the basic rate was accelerated, groups of beats began to disrupt the regular rhythm. These came in series of 2, 3 and 4 at a time, and resembled closely the periods of reexcitation seen in the accompanying records (fig. 5 *B*).

Unfortunately, observations on this particular patient had to be discontinued because of the onset of systemic toxic manifestations. There is good reason to believe, however, from other personal observations on similar patients with complete heart block, that ventricular fibrillation following the use of toxic doses of digitalis always appears after the basic ventricular rate has been gradually accelerated.

It is obvious from a study of innumerable electrocardiograms taken in both instances that the transitions from a lower ventricular rate to a higher one, with the accompanying variations in rhythm, are always initiated by an extrasystole. These extrasystoles initiating a new rhythm during the premonitory period are all of the supraventricular type (fig. 3 *E*). The extrasystoles initiating the periods of ventricular fibrillation, however, are always abnormal and are of an extremely wide deflection (figs. 5 and 6 *B*). This has also been observed experimentally, when transitions from one rate of the ventricles to another have been induced by a suitably placed extrasystole.[7]

Both the progressive increase in the rate of the beating of the ventricles, whether spontaneous or induced by digitalis, as well as the fact that the onset of each period of ventricular fibrillation observed in these studies was initiated by a distinct type of stimulus (an extra-

systole of a particular type) or the last of almost successive similar stimuli (fig. 4 *G, H*), as has been observed experimentally,[8] support the hypothesis that a circus movement underlies the mechanism of ventricular fibrillation.[9]

Further progress in such studies would be of value if there was a more intimate knowledge of the factors responsible for the spontaneous acceleration of the ventricles in patients with auriculoventricular dissociation subject to transient periods of ventricular fibrillation.

The present observations are still too meager to attempt a classification of the various stages of the fibrillatory contractions of the ventricles as pictured in the electrocardiograms. The drawbacks to such graphic interpretations have recently been well pointed out by Wiggers,[10] and the fact that most of the appended records were taken with lead *2* only is the more reason for postponing this phase of study and a comparison of these records with those obtained in animals.

It will suffice to state that the longest period of syncope observed in this case, that is, six minutes and two seconds, with spontaneous revival following it, as confirmed by the electrocardiograms, was associated with an acceleration of the ventricles that does not resemble very closely records of ventricular fibrillation observed in animals.

Of particular importance, in the light of recent researches,[11] was the mode of spontaneous recovery of the heart observed in this patient. At times fibrillation ceased promptly, a postundulatory pause followed, and revival was initiated by an idioventricular rhythm. Even when a postundulatory pause was not to be seen, recovery took place through the intermediary idioventricular rhythm, with impulses originating in a focus different from that of the basic ventricular rhythm. This sequence of events may bear some relationship to future studies in the therapy for ventricular fibrillation in man, since recovery somewhat similar in type to this mechanism has been seen by Wiggers[10] to follow the use of calcium with massage after all movements have ceased in a heart in which ventricular fibrillation had been induced experimentally by the intracardiac injection of potassium chloride solution.

8. Mines, G. R.: On Circulating Excitations in the Heart Muscles and Their Possible Relation to Tachycardia and Fibrillation, Tr. Roy. Soc. Canada, ser. 3 **8**:43, 1914. Levy, A. G.: The Relation Between Successive Responses of the Ventricle to Electric Stimuli and Ventricular Fibrillation, J. Physiol. **49**:54, 1914.

9. Mines (footnote 7). Garrey, W.: The Nature of Fibrillary Contraction of the Heart; Its Relation to Tissue Mass and Form, Am. J. Physiol. **33**:397, 1914.

10. Wiggers, C. J.: Studies of Ventricular Fibrillation Caused by Electric Shock: II. Cinematographic and Electrocardiographic Observations of the Natural Process in the Dog's Heart; Its Inhibition by Potassium and the Revival of Coordinated Beats by Calcium, Am. Heart J. **5**:351, 1930.

11. Wiggers, C. J.: Studies on Ventricular Fibrillation Produced by Electric Shock: III. The Action of Antagonistic Salts, Am. J. Physiol. **93**:197, 1930.

SUMMARY

1. A study was made of the electrocardiograms of a patient with auriculoventricular dissociation, who suffered from sixty-seven seizures of unconsciousness during a period of seven months while she was at the Montefiore Hospital.

2. Each syncopal seizure was associated with periods of ventricular fibrillation. The longest recorded attack with spontaneous recovery lasted six minutes and two seconds.

3. The alterations in the electrocardiograms preceding a syncopal seizure consisted of a gradual acceleration through steplike progressions of both the basic auricular and ventricular rates, the highest regular ventricular rate recorded being 65.2 beats per minute before ventricular fibrillation set in.

4. Periods of reexcitation of from 4 to 11 beats at a time were observed to appear during the premonitory period, heralding the approach of a seizure of unconsciousness.

5. The onset of every recorded seizure of ventricular fibrillation in this patient was initiated by a ventricular extrasystole which was always of the same character and arose from the same focus in the ventricle.

6. The ventricular rates during the periods of ventricular fibrillation varied from a minimum of 250 to a maximum of 1,000 beats per minute.

7. Spontaneous revival usually coincided with cessation of ventricular fibrillation. The mode of recovery was variable, but the restoration of the basic rhythm was preceded by an idioventricular rhythm, with a slightly irregular ventricular rate following, as a rule, a postundulatory pause.

8. Periods of unconsciousness in patients with auriculoventricular dissociation are associated with transient seizures of ventricular fibrillation much more commonly than has been suspected hitherto.

9. A clinical diagnosis of transient ventricular fibrillation may be suspected in such patients, if preceding a period of unconsciousness the heart rate has been noted to increase above that of the usual basic rate.

CHRONIC ARTHRITIS

WITH SPECIAL REFERENCE TO INTRAVENOUS VACCINE THERAPY *

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Much difference of opinion exists concerning what chronic joint diseases should be included in the term chronic arthritis. There are the changes, mostly proliferative, which from the anatomic appearance might well be considered infectious in nature. The relation of an infectious process to the joints showing retrogressive changes in the bone and cartilage is not so evident. Nichols and Richardson,[1] however, noted a decided overlapping in these two processes. The question arises whether the various anatomic proliferative and degenerative changes noted in nonspecific joint disease may not be different manifestations of a common injury. The finding of an etiologic agent would help in clearing up the concepts of chronic joint diseases. If an organism could be shown to have an etiologic relationship to the various anatomic forms of joint disease commonly called chronic arthritis, experiments toward combatting this organism could be started. With these ideas in mind and considering the recent experiments relative to intravenous vaccination in acute rheumatic fever,[2] the present work was started.

The purpose of the work reported in this paper was to study a series of patients with chronic arthritis in respect to classification, etiology and intravenous vaccine treatment. The chief emphasis was placed on the vaccine treatment.

MATERIAL

The patients were from the outpatient department of the University of Minnesota Hospital. In selecting cases for arthritic study, one chief criterion (joint pains) was followed. It was considered necessary that

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* From the Department of Medicine and the Department of Pathology, University of Minnesota.

1. Nichols, F. H., and Richardson, F. L.: Arthritis Deformans, J. M. Research **21**:149, 1909.

2. Clawson, B. J.: Experiments Relative to a Possible Basis for Vaccine Therapy in Acute Rheumatic Fever, J. Infect. Dis. **49**:90 (July) 1931.

the joint pains should have been present almost constantly for at least several months preceding the admission for treatment. In most cases, the pain had been present from one to twenty years. In nearly all, multiple joints were involved. The patients ranged in age from 18 to 78 years. The great majority showed joint involvement demonstrated by physical and roentgen examinations. Before the vaccine treatment was begun, most patients had the following examinations: A complete physical examination, including a Wassermann test and blood and urine studies, a roentgen examination of one or more joints, blood culture, a test for the agglutination titer of the serum with Streptococcus viridans, and an intracutaneous skin test with a suspension of Streptococcus viridans. One hundred patients with chronic arthritis have been treated up to the present time.

CLASSIFICATION

There has been much discussion of the etiology and classification of a large group of pathologic joint conditions. The etiologic factor has been well accepted in such cases as tuberculous, syphilitic, gonorrheal, traumatic and gouty joint involvement. Other joint conditions have met with much less universal agreement as to etiology and classification. This lack of agreement is illustrated by the following classifications commonly used:

British	American
I. Rheumatic fever	I. Rheumatic fever
II. Rheumatoid	II. Proliferative
	Infectious (roentgen)
	Atrophic
III. Osteo-arthritis	III. Degenerative
	Hypertrophic (roentgen)

Most authors have tended to draw a sharp line between rheumatic fever and the other arthritides. The chief causes for division have been: (1) the tendency of rheumatic fever to be complicated by endocarditis, which rarely occurs in more chronic forms of arthritis; (2) the tendency of the joint involvement in rheumatic fever to subside without obvious permanent damage. Many cases of so-called rheumatoid arthritis (proliferative, infectious, atrophic) are difficult to distinguish clinically from rheumatic fever. In some cases clinicians may wait several weeks or several months before making a diagnosis. The final diagnosis is influenced by the persistence of joint involvement or the presence of an endocarditis. A few patients with typical clinical rheumatic fever and, in some instances, an associated endocarditis may manifest progressive chronic joint disease. In our series we are unable to place a number of patients definitely in the accepted classifications, and we see a gradual graduation in clinical types from those termed

rheumatic fever to those termed degenerative arthritis. If the active infection has subsided the clinical manifestations are different than when the infection is persisting as it is in our series.

The roentgen findings in our series have shown all types of change. The degree of roentgen involvement cannot be taken as a definite guide of the clinical severity of a given case. The changes shown by roentgenography are much less marked in relation to the clinical condition present in younger than in older patients. Marked new bone formation is infrequent in young arthritic patients, while involvement of the synovial membrane and periarticular tissues is usually prominent. Secondary muscular atrophy often plays a prominent rôle in the disability present in many persons with arthritis, and this too is not evident from roentgen examination. The active infectious process in certain young patients may of itself clear up and leave them crippled for life with capsular and periarticular changes and muscular atrophy. In such a case there would probably never be new bone formation or a change in the roentgen appearance, even though the patient might live many years, unless a reinfection were to take place in later life. Later, under case reports, there will be given detailed roentgen findings in correlation with the clinical pictures present in persons with positive blood cultures. Roentgenography, while of definite value in determining certain types of joint damage, has also added to the general confusion of classification of joint disease.

ETIOLOGY

At present there is a decided lack of agreement in opinion concerning the etiology of chronic arthritis. Recent work strongly suggests the streptococcus as the active agent. In 1920, Richards [3] cultured the blood of 114 persons with chronic arthritis. Streptococcus viridans in pure culture was found in 14 (12.2 per cent).

Cecil, Nicholls and Stainsby [4] in two reports (1929 and 1931) stated that they had recovered streptococci from the blood of patients with chronic arthritis. In their last series of 154 cases of rheumatoid arthritis, they obtained streptococci from the blood in 96 cases (62.3 per cent). They also obtained streptococci from the joints in 33 of 49 cases (67.3 per cent).

In our series, blood cultures were obtained in 57 cases of unselected types of chronic arthritis and from 50 normal persons. The blood of both arthritic and normal persons was cultured in the same incu-

3. Richards, J. H.: Bacteriological Studies in Chronic Arthritis and Chorea, J. Bact. **5**:511, 1920.

4. Cecil, R. L.; Nicholls, E. E., and Stainsby, W. J.: The Bacteriology of the Blood and Joints in Chronic Infectious Arthritis, Arch. Int. Med. **43**:571 (May) 1929; The Etiology of Rheumatoid Arthritis, Am. J. M. Sc. **181**:12, 1931.

bator and examined in the same manner. The examiner had had no knowledge of the histories of the cases and could not, therefore, be prejudiced in the search for organisms. The blood of the normal persons was cultured as a control against contaminations from the air and the skin and to determine whether streptococci might be found frequently in blood cultures of all persons.

The technic [5] was the same as that used previously in culturing blood from patients having acute rheumatic fever. In 7 of the 57 cases of chronic arthritis, staphylococci were found in the blood cultures. Streptococci in pure culture were found in 25 of the remaining 50 cases (50 per cent). A positive streptococcus culture was obtained from one of the 50 normal persons (2 per cent). This person was found later to have had a pelvic infection when the blood for culture was taken.

One of the twenty-five strains of streptococci recovered from the blood of the patients with chronic arthritis was a typical hemolytic streptococcus. The remaining twenty-four either were of the viridans type or were inactive on the blood agar plate. They do not represent a special strain type. The organisms were seldom found in the culture mediums before the fifteenth day of incubation, and in some cases between the twenty-fifth and thirtieth days.

Our bacteriologic observations agree with the work of Cecil, Nicholls and Stainsby [4] in suggesting that the streptococci are an important etiologic factor in chronic arthritis.

IMMUNE REACTIONS

Two types of immune reactions (agglutinin and intradermal skin tests) to streptococci were studied in the patients with chronic arthritis. A comparison of these reactions was made in the arthritic patients before and after treatment.

The serums of 74 patients with chronic arthritis were tested for streptococcic agglutinins. The organism used was a strain of Streptococcus viridans isolated from the blood of a patient with acute rheumatic fever. A weak saline suspension of the organisms was mixed with increasing dilutions of the patient's serum in Wassermann tubes. The tubes were incubated in a water bath at 40 C. for two hours. The tubes were then removed from the bath and allowed to stand in a cool place for from eighteen to twenty hours, when the degree of agglutination was determined. The blood of all patients was tested before treatment was begun, and at the end of the course of treatment.

5. Clawson, B. J.: Studies on the Etiology of Acute Rheumatic Fever, J. Infect. Dis. **36**:444 (May) 1925.

The initial streptococcic agglutinating titer of the serums of 74 patients before treatment was found to average 1:132. The average titer after a course of treatment was 1:11,525. It is to be noted that the intravenous vaccine treatment brings about a decided rise in the concentration of agglutinins in the patient's serum.

Intradermal skin tests were made with the same strain of streptococcus that was used for agglutinating tests. Skin tests have been used by a number of persons in rheumatic fever and chorea, scarlet fever, measles, nephritis and chronic arthritis. Different strains of Streptococcus hemolyticus and viridans have been used by different investigators. Birkhaug [6] tested rheumatic, arthritic and normal persons with bacterial suspension, autolysates and filtrates of several streptococci of rheumatic origin. He found a higher percentage of positive tests in patients with rheumatic fever and chronic arthritis than in his series of controls. Apparently the bacterial suspension gave as satisfactory tests as the other methods. We have employed a bacterial suspension in our series.

Intradermal Skin Tests with Streptococcus Viridans

Conditions	Number	Positive	Per Cent
Chronic arthritis	127	112	91.8
Controls	107	53	49.6

Two strengths of bacterial suspension were used on each patient, one of 10,000,000 killed organisms per cubic centimeter, and another of 20,000,000 in physiologic solution of sodium chloride. One-tenth cubic centimeter was injected intradermally so that there were 2,000,000 organisms in one test and 1,000,000 in the other. A control wheal of 0.1 cc. of physiologic solution of sodium chloride was used in all cases. The results are shown in the accompanying table.

It is obvious from the results obtained that a positive skin test is of little significance in any individual case, but that in terms of percentages it is significantly higher in chronic arthritic patients than in a series of controls. A positive skin test probably indicates in most cases that the person is hypersensitive or allergic to the strain of streptococcus used in the test.

VACCINE TREATMENT

The application of the intravenous streptococcic vaccine therapy reported in this paper is based on previous experiments in animals,[2] and on the assumption that chronic arthritis for the most part is due

6. Birkhaug, K. E.: Rheumatic Fever: Skin Hypersensitiveness of Patients with Rheumatic Fever and Chronic Arthritides to Filtrates, Autolysates and Bacterial Suspensions of Streptococci, J. Infect. Dis. **44**:363 (May) 1929.

to a streptococcic infection and that patients having chronic arthritis are hypersensitive to that organism. The experiments showed that animals, made hypersensitive experimentally to streptococci, could be desensitized by the intravenous injection of a streptococcic vaccine, so that such animals could be protected from the development of further lesions when given subcutaneous injections of amounts of the organism that would produce extensive lesions in nonvaccinated hypersensitive animals. The subcutaneous injection of the vaccine did not desensitize or protect the animals, but, on the other hand, made them more hypersensitive. The work of Cecil, Nicholls and Stainsby [6] and the bacteriologic observations in our 50 cases supported the etiologic significance of the streptococci in chronic arthritis. The frequency of positive skin tests in such patients suggests that they are hypersensitive to streptococci. There is an evident similarity in the etiology and hypersensitiveness in the experimental hypersensitive animals and the patients with chronic arthritis. Since animals were protected, it was thought it might be possible to protect patients. With these considerations in mind, the experiments in vaccinating intravenously patients with chronic arthritis were begun. Clawson and Fahr [7] reported on the use of intravenous Streptococcus viridans vaccine in the treatment for rheumatic fever. Swift and his co-workers [8] have reported on the use of intravenous Streptococcus hemolyticus vaccine in the treatment for rheumatic fever.

METHOD

Intravenous injections were given to each patient at intervals of from five to seven days for the first five treatments, and at seven to fourteen day intervals for subsequent treatments. Routinely, the first dose was 100,000,000 killed organisms. The second dose in most instances was 300,000,000. The third dose was usually from 300,000,000 to 500,000,000. In most instances the dosage was reduced or held at the same amount, if the reaction following the previous injection had been severe. The fourth dose was usually from 500,000,000 to 1,000,000,000, depending on the patient's previous reaction. In some instances the dosage was not increased beyond 1,000,000,000, while in other instances as many as 3,000,000,000 or 5,000,000,000 were given. The reactions tended to be more marked with large dosage. It seems advisable now not to give more than 1,000,000,000 killed organisms.

7. Clawson, B. J., and Fahr, G. E.: Experiments Leading to a Possible Basis for Vaccine Therapy in Acute Rheumatic Fever, Proc. Soc. Exper. Biol. & Med. **27**:964, 1930.

8. Swift, H. F.; Hitchcock, C. H.; Derich, C. L., and McEwen, C.: Intravenous Vaccination with Streptococci in Rheumatic Fever, Am. J. M. Sc. **181**:1 1931.

These patients were all treated in the outpatient department, and were advised to go home immediately after the injection.

The following summaries of 20 cases in which the patients received vaccine therapy are inserted. Ten of these had positive blood cultures and 10 negative. We have included patients with and without clinical improvement while on therapy. The cases have been arranged to bring out the gradation in clinical types.

REPORT OF CASES

CASE 1.—*History.*—Mrs. E. P., aged 39, had had acute tonsillitis when 21 years of age (1913), and pains soon developed in most of the joints of her body. Transitory swelling and redness were present in the involved joints and she had a fever. She was confined to bed for three weeks. Her physician made a diagnosis of "inflammatory rheumatism." Shortly afterward, he told her that a heart murmur was present. Since then, she had had joint pains off and on most of the time. Seven months before this report (June, 1930), her joints became much worse and remained painful. She had involvement especially in her knees and fingers, and had some swelling in these joints much of the time. She had been up and about for the most part, but had marked pain at times.

Examination.—There was a definite presystolic murmur over the apex of the heart, and the heart was enlarged, with a mitral contour. There was swelling of many of the metacarpophalangeal and phalangeal joints. Both knees were swollen, and the left knee was tender to pressure, as was the right wrist. Roentgen examination of the right wrist was reported as follows: "There is slight atrophy of the bones and some slight cartilaginous absorption, especially in the radiocarpal joint. The appearance suggests an atrophic arthritis of the periarticular type with very little involvement of the joints as yet. Conclusions: atrophic arthritis, periarticular type." A blood culture showed Streptococcus viridans.

Vaccine Therapy.—The patient received nine injections of vaccine, in doses of from 100,000,000 to 500,000,000 organisms at weekly intervals. Reactions, consisting of moderate fever and chills of a few hours' duration, came on about three hours after each injection. No improvement followed the first three injections. Since then, the pain has been much reduced, and she is able to do much more physical work than prior to treatment. The agglutination titer was raised from 1:0 to 1:12,800 after six injections.

CASE 2.—*History.*—In Mrs. R. L., aged 35, joint pains had been present for five months with swelling and redness at times. This condition had progressively involved the right shoulder, hands, wrists, fingers and feet. The finger involvement was transitory, there being swelling, pain and redness of four or five days' duration. She had not been confined to bed.

Examination.—The temperature was 99.6 F. No gross deformity, swelling or redness of joints was noted at this time. There was some limitation of motion of the left shoulder. A roentgenogram was not obtained. A blood culture gave negative results.

Vaccine Therapy.—The patient received eight injections of from 100,000,000 to 3,000,000,000 organisms, over a period of two months. On most occasions she had no reaction following the injection. The first reaction followed the fifth dose of 3,000,000,000 and consisted of slight chills and fever for a few hours. The joints were definitely less painful after the third injection, and the patient stated

that she felt much better generally. The agglutination titer was raised from 1:0 to 1:6,400 after six injections.

CASE 3.—*History.*—Mr. M. M., aged 22, first noticed pain in the hips and spine four years before this report. Eighteen months before, soreness developed in the right shoulder. During the past six weeks the knees had been definitely painful. He now had marked difficulty in walking and took short steps. During the past six weeks he had been sleeping very poorly because of pains; he had been unable to work the past month.

Examination.—The patient was unable to extend the thighs at the hips because of pain. Tenderness was present over the hips and knees. Limitation of motion of the spine was present. Roentgen observations on the right hip and left knee were: "Some suggestion of arthritis in the right sacro-iliac region; otherwise negative." A blood culture gave negative results.

Vaccine Therapy.—The patient received five injections over a period of one month. The doses were from 100,000,000 to 2,000,000,000 organisms. The reactions were chiefly slight chills and fever of from two to three hours' duration. The joints were slightly improved after the second injection and much improved after the third. At that time the patient was able to return to work after being out for a month because of joint pains. The pain was practically all gone after the fourth injection.

CASE 4.—*History.*—Miss M. A., aged 18, first noticed pain in the toes of the left foot two years before this report. Since that time the feet, ankles, knees, hips, fingers, hands, wrists, elbows and shoulders had been involved. The joints had frequently been swollen, tender and warm. She had had no fever. The joints had tended to be acutely involved in succession and partially cleared up after a few days to a few weeks.

Examination.—Limitation of motion was present in the left arm at the shoulder. The wrists were definitely swollen and tender to touch. There was definite limitation of motion at the wrists. The left knee and the feet were moderately swollen. Roentgen observations on the left knee and right wrist were: "There is some atrophic arthritis involving the right wrist and the left knee. Slight cartilaginous destruction and some bone destruction are also present. Conclusions: atrophic arthritis, fairly marked degree, right wrist and left knee." A blood culture gave negative results.

Vaccine Therapy.—The patient received twelve injections over a period of two and one-half months of doses of from 100,000,000 to 3,000,000,000 organisms. The reactions varied from none to moderate chills and fever for a few hours. There was perhaps less joint pain after two injections, and much less pain was noted after four injections. Five days after the sixth injection, the patient had pain and was unable to walk for five days because of swollen, painful ankles. The agglutination titer was depressed to 1:0 at that time. Seven hours after the seventh injection, the swelling in the feet had subsided and the patient could walk about freely. She was practically free from joint pains while under weekly injections during the following six weeks. Skin tests, positive before treatment, were very faint after five injections. The agglutination titer was raised from 1:200 to 1:6,400 after five injections.

CASE 5.—*History.*—Mrs. C. B., aged 39, had noticed multiple joint pains in the left shoulder, left hip, left foot, lower part of the spine and right temporomandibular joint for about three months (since October, 1930). No redness or swelling was seen in any of the joints. She had been working as a scrubwoman. This work had been very difficult recently because of the joint pains.

Examination.—No definite swelling or deformity was present. The roentgen report was: "Left ankle negative; lumbosacral spine negative." A blood culture yielded Streptococcus viridans.

Vaccine Therapy.—Six injections ranging from 100,000,000 to 600,000,000 organisms were given at from four to seven day intervals. On two occasions there were no reactions; at other times she had chills of three to four hours' duration. She had a temperature of 102 F. on one occasion. The pain in the left hip, present constantly, disappeared after the third injection; there was much less pain in all joints after four injections, and the patient was able to perform her duties as a scrubwoman much more easily. The condition was still improved after two and one-half months. The agglutination titer was raised from 1 : 50 to 1 : 6,400 after five injections.

Case 6.—*History.*—Miss E. J., aged 27, developed a pain in the right shoulder, about nine years before this report (1922), which disappeared after a few months. She then began to have pains in her feet and hands with definite swelling, redness and local heat. Since then she had had involvement of both shoulders, elbows and knees. She continued to have joint pains. Her pain had been somewhat alleviated by a series of general diathermy treatments.

Examination.—There was fairly marked deformity of both hands, owing to involvement of the phalangeal and metacarpophalangeal joints. There was almost complete fixation of the left elbow at a 60 degree angle and some fixation of the right elbow and right hip. Swelling was present over some of the joints, and there was tenderness on pressure. Roentgen examination of the left elbow was reported as follows: "There is a marked loss of cartilage, and considerable destruction, especially in the upper ends of the radius and ulna, is present. A small amount of new bone formation has also taken place, but this is minimal. Conclusion: chronic atrophic arthritis." A blood culture yielded Streptococcus viridans.

Vaccine Therapy.—Twelve injections were given at one week intervals. The dosage was run up from 100,000,000 to 1,000,000,000 organisms in four injections. It was then reduced to 300,000,000 for subsequent treatments. Reactions varied from very slight reactions to chills and fever for four or five hours, and increased aching for twenty-four hours after the injection. The joints remained about the same throughout with the usual fluctuation in pain. The skin tests, positive before treatment, became negative. The agglutination titer was raised from 1 : 800 to 1 : 25,000 after six injections.

Case 7.—*History.*—Mrs. A. J., aged 43, first noticed swelling and pain in both knees one year before this report (January, 1930); no redness was present. The pain had been present constantly and was aggravated by walking. Six months later her fingers became similarly involved, and she also had pain through her arms. The past three or four months she had noticed swelling and pain in the feet and ankles. At the time of examination the pain was most marked in the fingers and hands.

Examination.—Both wrists were slightly enlarged, the left more markedly; they were very tender on pressure. Local swelling appeared over many of the finger joints. The other joints were tender on pressure but showed no gross deformity. Roentgen observations on the right hand were: "Slight to moderate atrophy of the bones; no particular involvement of the joints themselves. The appearance would suggest a slight amount of periarticular arthritis." A blood culture gave negative results.

Vaccine Therapy.—The patient received eleven injections over two and one-half months, ranging from 100,000,000 to 2,000,000,000 organisms. On some

occasions there were no reactions; again there were moderate chills and fever of from thirty minutes to three hours' duration. The joints were less painful after four injections. Since then they have remained definitely less painful than before therapy, though with some exacerbations. The agglutination titer was raised from 1:0 to 1:400 after six injections.

Case 8.—*History.*—Mrs. M. H., aged 61, had had pains in many joints since 10 years of age. These had been much worse during the past seven years (since 1924). She now had pain and swelling in the hands and fingers, elbows and left shoulder and over the cervical spine; these symptoms were most marked in the right hand and elbow.

Examination.—There were definite swelling and slight fluctuation of the right elbow; limitation of movement and marked pain were noted on movement. Some swelling and tenderness were present in some of the right finger joints and there was tenderness over the right hand. Motion of the right wrist was painful. Roentgen observations on the right elbow were: "There is some atrophy of the bones about the elbow joint and also a few very small spurs. There is only very slight narrowing of the joint space itself, the change being chiefly periarticular. Conclusion: arthritis of right elbow joint, periarticular type." A blood culture gave negative results.

Vaccine Therapy.—The patient received seventeen injections over a period of nearly four months at five to ten day intervals. The doses were from 100,000,000 to 500,000,000 organisms. Reactions were present after most injections, usually chills and fever of from three to six hours' duration. Nausea occurred with some reactions. No definite relief was consistently present. Periods of possible improvement occurred. Intradermal skin tests showed nodules which persisted for six weeks. Skin tests, applied after six injections, were negative. The agglutination titer was raised from 1:400 to 1:12,800 after seven injections.

Case 9.—*History.*—Mrs. E. M., aged 61, had had joint pain for the past forty years. This had been present in nearly all of her joints, although there had never been any redness or swelling. Recently she had had marked pain in the knees and some swelling at times.

Examination.—Moderate swelling of the knees was observed. There were no gross deformities of any joints. Roentgen examination of the left knee was reported as follows: "Slight evidences of static arthritis are present, but no other evidence of pathology. Conclusion, slight static arthritis." A blood culture gave negative results.

Vaccine Therapy.—The patient received thirteen injections of from 100,000,000 to 3,000,000,000 organisms over a period of nearly four months. Most of the reactions consisted of slight chills and fever for two to three hours. There was some relief from pain after the first injection and definite relief after three injections. The patient is doing housework and has recently been able to do a complete washing for the first time in two years. Increased motion in the arms is now present. The agglutination titer was raised from 1:0 to 1:6,400 after three injections, and remained at that level after eight injections.

Case 10.—*History.*—In Mrs. A. R., aged 63, pain was present in the right knee for about fifteen years. Stiffness was also present. These symptoms were aggravated by the patient's being on her feet a great deal; the knee was more painful in the evening than in the morning; there was no other joint involvement and no history of any injury. The patient was always of less than average weight. She had a tendency toward constipation and functional gastro-intestinal symptoms.

Examination.—General findings were essentially negative. Roentgen examination of the right knee was reported as follows: "There is a definite narrowing of the medial portion of the joint space, such as is commonly associated with a static arthritis. There is a small amount of bone production around the patella and the tibia, characteristic of a chronic hypertrophic arthritis. Opinion: Static arthritis with hypertrophic bone production." A blood culture gave negative result.

Vaccine Therapy.—The patient received eight injections of from 100,000,000 to 1,000,000,000 organisms over a period of more than two months. Reactions consisted of slight chills a few hours after injections. On one occasion some diarrhea was present. The knee began to be slightly less painful after the third injection and has continued to improve since that time, so that there is much less pain at the present time and walking is definitely easier. The agglutination titer was raised from 1:200 to 1:12,800 after five injections.

CASE 11.—*History.*—Mrs. A. J., aged 29, had had pain in the left hip for the past two months so that walking was painful and difficult. There was some pain in other joints, especially the left knee.

Examination.—The patient walked with a definite limp. Pain was present over the hip on abduction of the thigh. Roentgen examination of the left hip and left knee was reported as follows: "There is a very slight hypertrophic change around the left hip, suggesting an old, rather low grade arthritis. A small amount of effusion is present in the left knee. Conclusions: effusion of left knee; slight hypertrophic arthritis of the left hip." A blood culture gave negative results.

Vaccine Therapy.—The patient was given ten treatments over a period of three months at intervals of from four to twenty days with doses of from 100,000,000 to 4,000,000,000 organisms. Most of the last doses were from 1,000,000,000 to 2,000,000,000. Slight or no chills and fever occurred after most injections; this reaction was quite marked for seven hours after the dose of 4,000,000,000. The joints were definitely less painful after four injections, and after that time the patient walked without a limp. She stated recently that there is now only occasional joint pain and that she is much improved. Skin tests have remained positive. The agglutination titer was raised from 1:0 to 1:3,200 after seven injections.

CASE 12.—*History.*—A. G., aged 57, had had joint pains for years; they began in the knees and elbows and extended to nearly all the joints. He was in the hospital in 1921 for this condition, at which time there was slight limitation of motion in the right shoulder, elbows and wrists. At that time he had all infected teeth removed, and tonsillectomy was done. A roentgenogram of the knees was made at that time (1921) and interpreted as follows: "Moderate hypertrophic changes involving the articular surfaces. Conclusions: hypertrophic arthritis, both knees."

Examination.—The patient walked with some difficulty, using a cane. He had limitation of motion of the knees, hips, wrists, elbows and shoulders. Roentgen observations in 1931 were: "There is a considerable loss of the articular cartilage in the right knee joint with some evidence of new bone formation. The appearance is quite characteristic of an infectious arthritis in the stage of repair. Only a slight narrowing of the right ankle joint with considerable atrophy of the bone. The change appears to be chiefly periarticular. Conclusions: infectious arthritis, right knee joint; probable periarticular arthritis, right ankle joint." A blood culture yielded Streptococcus viridans.

Vaccine Therapy.—Thirteen injections were given over a period of three months at one week intervals. The dose was from 100,000,000 to 2,000,000,000 organisms. Reactions varied from moderate chills and fever for twenty minutes to more severe chills and fever for four or five hours. There has been no definite improvement in joint pain or stiffness. The agglutination titer was raised from 1:200 to 1:12,800 after seven injections.

CASE 13.—*History.*—Mrs. C. M., aged 61, had had persistent pain in the region of the thoracic spine for six years (since 1925). Pain often would waken her at night and was present at all times when she was working. She had also had slight pains in the ankles and knees during the past four years. These pains were inconstant and not severe, and were noticed chiefly on damp rainy days.

Examination.—Limitation of motion of the thoracic spine was observed. Other joints showed no changes. The roentgen report was, "Thoracic spine: There is a marked scoliosis of the thoracic spine. There is some evidence of atrophy of the bodies. There is only a slight amount of hypertrophic arthritis present." A blood culture showed Streptococcus viridans.

Vaccine Therapy.—Fourteen injections were given over a period of three months at one week intervals. The dosage was from 100,000,000 to a maximum of 2,000,000,000 organisms, the last eight injections being 2,000,000,000. The patient had no reaction from the first two injections. With the larger dosage she had no reactions at times, but at other times had chills and fever for three or four hours. Herpes labialis was noted on one occasion and increased aching for a few hours on another occasion. She had no relief until after five injections. Since that time, the previous moderate pain in the extremities has subsided, and the severe backache has entirely disappeared for the first time in six years. While previously unable to walk more than two blocks because of severe back pain, she can now walk several miles. Some residual stiffness persists through the thoracic spine, but there is no severe pain. The agglutination titer was raised from 1:0 to 1:200 after two injections.

CASE 14.—*History.*—Mrs. T. D., aged 64, had had marked pain and swelling in the knees for the past six months. The pain was worse on motion after a rest period.

Examination.—The patient walked with a limp. The knees were definitely tender and swollen. Roentgen observations on the left knee were: "There is a slight degree of chronic hypertrophic arthritis, involving the left knee joint and the patella. There is no evidence of destruction of cartilage or of bone. Conclusion: slight chronic hypertrophic arthritis." A blood culture was negative.

Vaccine Therapy.—The patient received thirteen treatments over a period of three and one-half months. The dosage varied from 100,000,000 to 5,000,000,000 organisms. The last four doses were reduced to 3,000,000,000. Reactions were variable; none was present until a dose of 1,000,000,000 was used. With a larger dosage she had no reaction at times, and at other times chills and fever of from two to four hours' duration. After the second injection, the pains were much lessened and swelling subsided in the knees. Improvement has continued. Skin tests, strongly positive before treatments, became negative after three injections and remained negative when rechecked after five injections. The agglutination titer was raised from 1:100 to 1:800 after two injections.

CASE 15.—*History.*—Mrs. C. V., aged 78, first noticed pain in the knees ten years before this report (1921). The pain became quite severe, and she used crutches for seven years, discarding them three years ago. A roentgenogram taken in 1921 showed a definite hypertrophic arthritis of the right knee. During the

past ten years the patient had never been free from joint pains, especially of the hands. She stated that swollen tender lumps appeared over the phalangeal joints and persisted for several months, leaving hard, painless lumps in their place.

Examination.—Some swelling and tenderness were noted over the knees, especially the right. There was some enlargement of many of the phalangeal joints. There were a few tender soft masses over some of the phalangeal joints. One of these was removed, and section showed a small cyst with an inflammatory wall. Roentgen observations on the right knee (1921) were: "Definite new bone formation characteristic of hypertrophic arthritis." A report on the left hand (1931) was: "There is a distinct loss of cartilage in the interphalangeal joints with some hypertrophic changes. Slight loss of cartilage is present in the wrist joint. The appearance suggests a chronic arthritis of the hypertrophic type mixed with the atrophic type. Conclusions: atrophic and hypertrophic arthritis, left hand." A blood culture showed Streptococcus viridans.

Vaccine Therapy.—The patient received nine injections over a period of two months at one week intervals. The doses varied from 100,000,000 to 400,000,000 organisms. At times no reaction followed; at other times, moderate chills and fever; on one occasion the patient had chills for three hours and fever for four hours. The joints were less painful after the second injection and have continued to be less painful since that time. The patient also walks more easily and with very little limp. Intradermal skin tests, which were positive before treatment, were negative when tested after seven injections. The agglutination titer was raised from 1:400 to 1:25,000 after eight injections.

CASE 16.—*History.*—Mr. M. E., aged 71, fell thirty-five years ago and struck the left shoulder. He was able to work immediately afterward. Two years later he developed pain in that shoulder and had had pain constantly since. He was unable to put on his coat without help because of the pain. He had tried many types of medication without relief. No other joints were involved.

Examination.—There was limitation of motion in the left arm at the shoulder. Roentgen observations on the left shoulder were: "There is a marked chronic hypertrophic change about the acromioclavicular joint, especially involving the acromion process. The appearance suggests most strongly an old injury with secondary changes, but the possibility of hypertrophic arthritis must be strongly considered. Conclusions: hypertrophic arthritis or old injury of left acromioclavicular joint." A blood culture showed Streptococcus viridans.

Vaccine Therapy.—The patient received five injections of from 100,000,000 to 2,000,000,000 with no reactions or relief from pain.

CASE 17.—*History.*—Mrs. B. S., aged 57, had had pain and, at times, swelling in many joints for ten or twelve years. The hands had frequently been involved, and there had also been some pain in the knees, ankles and shoulders. During the past two weeks, the soreness had been more marked, especially in the left knee.

Examination.—The patient walked with a limp. Some swelling and tenderness were present over the left knee. Roentgen observations on the left knee were: "There is a fairly marked hypertrophic arthritis, involving the left knee joint, with a number of spurs projecting from the tibia and patella. Conclusions: chronic hypertrophic arthritis." A blood culture yielded Streptococcus viridans.

Vaccine Therapy.—The patient received nine injections, from 100,000,000 to 2,000,000,000 organisms, over a period of two and one-half months. The reactions varied, the patient usually having chills and fever of about four or five hours' duration; on one occasion she had some fever for a day. The joints were less painful after the second injection, and the swelling in the knees definitely sub-

sided. The patient has markedly improved; she walks easily and with very little pain. Skin tests, previously positive, became negative after five injections. The agglutination titer was raised from 1:100 to 1:12,800 after five injections.

CASE 18.—*History.*—Mr. U. G. S., aged 68, had had pain in the knees and in the back for the past seven years (since 1924). There had also been some pain in the shoulders, elbows and feet, though less marked.

Examination.—The patient walked with a slight limp. No gross joint deformities were observed. The roentgen report on the lumbosacral region was: "There is a marked degree of chronic hypertrophic arthritis, involving the whole lumbar spine. Conclusion: chronic hypertrophic arthritis." A blood culture showed Streptococcus viridans.

Vaccine Therapy.—The patient received nine injections of from 100,000,000 to 2,000,000,000 organisms at weekly intervals over a period of two months. Reactions either were absent or consisted of slight chills and fever; the patient was always up and about. No improvement whatever occurred until after five injections, after which time the pain was much less marked and remained so. The patient now has no pain at night and sleeps well. Pain is absent except after hard work as a gardener.

CASE 19.—*History.*—Mrs. H. L., aged 75, had had pain through the back for three or four years. There was no pain elsewhere.

Examination.—General findings were negative except for moderate hypertension. There was moderate fixation of the spine, with limited movement. A roentgenogram of the spine and lumbosacral region showed "definite new bone formation and lipping, characteristic of hypertrophic arthritis." A blood culture gave negative results.

Vaccine Therapy.—Over a period of two and one-half months the patient received nine injections (100,000,000 to 1,000,000,000). Reactions varied from no chills to chills and fever of from three to five hours' duration and, on one occasion, marked herpes labialis. The backache was definitely better after the second injection, and little or no pain has been present since then, though some stiffness and limitation of motion of the spine persist. The agglutination titer was raised from 1:200 to 1:1,600 after six injections.

CASE 20.—*History.*—Mrs. J. F., aged 63, first noticed pain in her right hip seven years before this report, and began to limp at that time. She believed that her right leg was getting shorter. She had had some gradual extension of pain into the spine and had become slightly stooped. She stated that her mother had a similar condition with pains in the hip joints.

Examination.—There were limitation of motion in the right hip and tenderness over the right hip and lumbar spine. The patient walked with a limp. Kyphosis was present. The roentgen report was, "Thoracic spine, pelvis, femurs, lumbar spine: Plates of the spine showed a marked kyphosis with some hypertrophic change. Several of the vertebrae, most particularly the twelfth thoracic, show a characteristic change typical of Paget's disease, there being some degeneration and some marked increase in the trabeculae and increased density. The same process is present to a lesser degree throughout the rest of the thoracic and the lumbar vertebrae. Plates of the pelvis show a very marked characteristic Paget's disease, involving especially the whole upper half of the right femur and pelvis of this side. On the left the ilium, sacrum, and to some extent the pelvis are involved, but the femur is not involved. The sacrum throughout is fairly well involved. There is excessive calcification and irregular distribution throughout.

There is some calcification of the intervertebral discs. Conclusions: generalized Paget's disease or osteitis deformans." A blood culture yielded Streptococcus viridans.

Vaccine Therapy.—The patient received twelve injections of from 100,000,000 to 1,000,000,000 organisms. The usual reactions were slight chills and fever of a few hours' duration. The joints were definitely less painful after the fourth injection and have continued to remain improved. The patient feels stronger and can walk better since receiving the vaccine. The agglutination titer was raised from 1:200 to 1:6,400 after five injections.

REACTIONS

Immediately following an injection, the patients experienced no reaction that might correspond with the so-called anaphylactic reaction which sometimes follows injections of horse serum. Usually about three hours after the injection, there was a general reaction. Occasionally, this would follow within an hour or occur as much as seven or eight hours afterward. This reaction consisted of chills of varying degree and duration, followed by fever. The chills were usually of one or two hours' duration and the fever of two or three hours' duration. The reaction, however, was by no means constant. Sometimes it might be of little consequence and at other times it might be severe and continue for from twelve to fourteen hours. The temperature, when elevated, was usually from 100 to 101 F., although it was as high as 104 F. in a very few instances. Following about 25 per cent of the injections, there was little or no reaction. In a few instances there would be severe aching at the time of the reaction, especially a backache, although this was present in a minority of cases. Nausea, vomiting and diarrhea were sometimes present. Patients occasionally felt tired and weak the following day, but more often they were inclined to feel no ill after-effects, and in many cases, felt much better.

RESULTS OF TREATMENT

The psychologic factor must be strongly considered in determining the results of any therapeutic measure for arthritis. An attempt was made to eliminate this from consideration as much as possible. The majority of patients had had arthritis for years and had tried many types of medication, diathermy and other physical thererapeutic measures. Some had had previous treatments with typhoid vaccine with almost unanimous disappointment. The criteria indicative of improvement were: (1) decreased pain, (2) definitely increased motility of joints, (3) ability to return to work and (4) statements from the patients that there had been no recent spontaneous period of sudden improvement comparable with that experienced since being on vaccine therapy. From the foregoing criteria it seemed that about 75 per cent of the patients under-

going treatment reported definite improvement. The remaining 25 per cent showed no improvement and, possibly, in a few instances became worse, though probably not worse than would be expected in their clinical course without treatment. The patients who were helped showed a rather definite tendency toward improvement after a given number of injections.

Analysis of the time of beginning clinical improvement is as follows:

1 treatment	5 per cent improved
2 treatments	47.5 per cent improved
3 treatments	70 per cent improved
4 treatments	71.7 per cent improved

After the fourth injection there was little or no further increase in the percentage of patients showing clinical improvement. Some of the patients who were clinically unimproved had as many as from fifteen to twenty injections without benefit. Those who enjoyed clinical improvement in nearly every instance maintained that improvement during the course of therapy. At this time no definite conclusions as to the permanence of this improvement can be drawn. In some instances the improvement has been transitory, while in other instances it has persisted for one to two months after the last injection. There seems to be an individual variation in the duration of improvement after therapy. This improvement apparently can be maintained by repeating the injections at intervals of from seven to fourteen days.

The agglutination titer rose from an average of 1:132 before treatment to an average maximum titer of 1:11,525 after therapy. The highest agglutination titer after therapy in our series was 1:25,000, and this was obtained in several cases.

The intradermal skin tests were also observed in 25 cases before treatment and after five or more injections. The tests were positive before treatment in every instance. After treatment, nine became negative, six were definitely reduced, and ten remained positive as before the vaccine therapy.

COMMENT

One hundred cases of chronic arthritis were studied in respect to classification, etiology and intravenous vaccine treatment. The chief emphasis is placed on the treatment.

It is difficult to classify these 100 cases of chronic arthritis into definite groups by clinical and roentgen findings. There seems to be a gradual gradation in clinical types from the typical rheumatic arthritis to the degenerative type. There are all kinds of borderline and mixed cases, according to the standard classifications in use at the present time.

The frequency of the presence of the streptococci, usually the viridans strains, recovered from the blood of chronic arthritic patients,

would strongly suggest that in most cases chronic arthritis is infectious in character and is generally due to streptococcic infection. The streptococci are frequently recovered from the blood of patients with the various nonspecific forms of arthritis, such as acute rheumatic arthritis, rheumatoid (proliferative, atrophic) arthritis and ostearthritis (degenerative, hypertrophic arthritis). It appears that the various clinical types of arthritis may be different manifestations in the pathogenesis of chronic arthritis due to streptococci. There seems to be a general variation in the type of response to infection with different age groups; children most frequently manifest clinical rheumatic fever and the older adults more often develop new bone formation.

The results obtained from vaccine treatment are evaluated from two different angles: 1. By intravenous vaccination two conditions seem to be produced in the patient which are conspicuous in protected animals. There is evidence that the patients who are hypersensitive to streptococci tend to become desensitized, as indicated by a positive skin test becoming negative, and regularly there is a marked increase in the concentration of the streptococcic agglutinins in the patients' serums. Desensitization and a marked increase in the agglutinating titer of the serum are the two conspicuous things noted in vaccinated hypersensitive animals, which are protected from the development of further lesions. 2. The second means of estimating the value of intravenous vaccine therapy in chronic arthritis is the fact that about 75 per cent of the patients become clinically improved, as indicated by a relief from pain, an increase in the motility of the joints, ability to go back to work, etc.

The mechanism of protection is not determined. Two factors are suggested: a desensitization as indicated by the change in the skin test and antibody protection as suggested by the increased agglutinating titer.

Protein shock as a possible beneficial factor must be considered. Experiments in animals indicated that the protective phenomenon was not due to nonspecific protein shock. The results from typhoid vaccine in patients with chronic arthritis were much less favorable, and the reaction much more severe, than when a streptococcic vaccine was used. The clinical improvement in the patients vaccinated with streptococci had no apparent correlation to the amount of shock. In many cases the improvement was most marked when shock was absent.

The protective phenomenon, as indicated by previous experiments, does not seem to be type-specific, but it does seem to be species-specific: Streptococcus hemolyticus protected against Streptococcus viridans. The protection appears not to be due to nonspecific protein shock. Injections of typhoid vaccine did not protect against Streptococcus viridans.

No definite conclusions can be drawn as to the permanence of the results from intravenous vaccine therapy in chronic arthritis. It may be of only temporary value and may necessitate frequent injections over a long period of time to maintain the improvement. Further observations over a long period are necessary to determine the value of this method of treating patients for chronic arthritis, but we know of no other therapy that has given similar clinical improvement in as high a percentage of cases.

CONCLUSIONS

1. The types of arthritis in our series do not fit accurately into any classification now in use. There seem to be many mixed types and a gradation in the clinical picture from rheumatic fever to ostearthritis (degenerative, hypertrophic).

2. The frequent occurrence of streptococci in the blood stream of patients with various clinical forms of chronic arthritis strongly suggests an etiologic relationship.

3. Intravenous streptococcic vaccination brings about in patients two conditions (desensitization and a high agglutinating titer) that are regularly associated with the protection experimentally developed in animals against streptococci by intravenous vaccination. This analogous condition in vaccinated patients and animals affords a basis for intravenous vaccination in patients having chronic arthritis.

4. Since subcutaneous injections of streptococci in animals tend to increase hypersensitiveness and only produce a low agglutinating titer in the serum, the subcutaneous method of vaccination in chronic arthritis would seem to be of less value than the intravenous method, if not contraindicated.

5. No ill effects have resulted from the intravenous vaccinations in the 100 cases studied. On the other hand, in 75 per cent of the cases the clinical improvement appears to be sufficient to justify the further use of this method of treatment for chronic arthritis.

THIOCYANATE THERAPY IN HYPERTENSION

I. OBSERVATIONS ON ITS TOXIC EFFECTS *

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Since Pauli's [1] observation in 1903 that thiocyanate is effective in reducing high blood pressure, the use of this drug has apparently gained favor. Frequent confirmation of this observation, particularly in recent years, seems to have caused rather general acceptance of thiocyanate therapy as offering, in a selected group of persons with hypertension, a method of meeting a difficult therapeutic problem. Ever since Claude Bernard's [2] first pharmacologic investigation, in 1857, there have been many references to the toxic properties of thiocyanate, but in examining the literature it is noteworthy that, with a few exceptions, mainly its hypotensive property is stressed. The appearance of toxic manifestations thirteen times in a series of seventy-four trials in fifty patients under investigation by us seemed of sufficient importance to report. In two of these thirteen patients there was a fatal outcome. We believe that this is the first report of death in man from thiocyanate administered for therapeutic purposes.

Westphal and Blum [3] administered 0.5 Gm. three times a day for eight to twelve days in nine patients and noted a tendency to respiratory inflammations, muscle weakness and psychosis. They reported no deaths. Takacs [4] reported a papular dermatitis following the administration of 1 Gm. daily for nine days. Weiss and Ruedemann [5] and

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1. Pauli, W.: Ueber Ionenwirkungen und ihre therapeutische Verwendung, München. med. Wchnschr. **50**:153, 1903.

2. Bernard, Claude: Leçons sur les effets des substances toxiques et médicamenteuses, Paris, J. B. Baillière et fils, 1857, p. 354.

3. Westphal, K., and Blum, R.: Rhodan Treatment of Genuine Arterial High Pressure and the Theoretical Foundation for It, Deutsches Arch. f. klin. Med. **152**: 331, 1926.

4. Takacs, I.: Versuche mit Rhodansalzen: 1. Einfluss der Rhodan auf Magensekretion, weisse Blutkörperchen, Pulsschlage und Blutdruck, Ztschr. f. d. ges. exper. Med. **50**:432, 1926.

5. Weiss, C. R., and Ruedemann, R.: Exfoliative Dermatitis from Potassium Sulphocyanate Therapy, J. A. M. A. **93**:988 (Sept. 28) 1929.

Ayman [6] had a similar experience. A complete summary of the known facts concerning the pharmacologic properties of thiocyanate was presented by Nichols.[7] His observations on the toxic effects of the drug in guinea-pigs closely paralleled the clinical manifestations in two fatal cases in man observed by us. He collected the reports of four fatalities in man from the literature, in which thiocyanate was taken accidentally or with suicidal intent. The fourth case that he quoted [8] presented a clinical syndrome practically identical with manifestations noted in our fatal cases. He recommended as a safe dose in man 1 Gm. daily. Nerking,[9] on the other hand, noted toxic effects with doses of from 0.5 to 1 Gm. daily. Gager,[10] in a series of thirty-five patients, noted dermatitis in two instances and weakness in one other as the only toxic manifestations. The dosage used was 0.3 Gm. daily for one week, 0.2 Gm. daily for one week and 0.1 Gm. daily for one week. Thereafter 0.1 Gm. was given daily or every other day except in obstinate cases, in which 0.3 Gm. was given for several weeks. Fineberg [11] treated twenty-one patients with 1 Gm. of thiocyanate daily for three months and noted no toxic effects. Palmer, Silver and White,[12] using the dosage described by Gager, noted a few instances of weakness and cardiac pain. In a group of twenty-four patients studied by Borg,[13] unpleasant symptoms developed in thirteen. Toxic psychosis developed in four. There were disorientation, hallucination of sight and hearing, mania, confusion and delusions of persecution. These four patients had received larger doses than the rest. Recovery occurred in all, in from five to seven days after the drug was discontinued. The dosage used in his study was from 0.13 to 0.65 Gm. three times daily for from one to four weeks.

This review of the literature is sufficient to indicate, first, that the toxic effects of thiocyanate in man are known and have been repeatedly observed by independent investigators, and second, that while a given dose proves harmless and perhaps therapeutically effective in the hands

6. Ayman, D.: Exfoliative Dermatitis from Potassium Thiocyanate, Correspondence, J. A. M. A. **93**:1671 (Nov. 23) 1929.

7. Nichols, J. B.: Pharmacologic and Therapeutic Properties of the Sulphocyanates, Am. J. M. Sc. **170**:735 (Nov.) 1925.

8. Vintilesco, J., and Popesco, A.: Ann. d'hyg. **25**:239, 1916.

9. Nerking, J.: Toxic Action of Thiocyanates, Deutsche med. Wchnschr. **39**: 945, 1913.

10. Gager, L. T.: The Incidence and Management of Hypertension, with a Note on Sulphocyanate Therapy, J. A. M. A. **90**:82 (Jan. 14) 1928.

11. Fineberg, M. H.: Potassium Thiocyanate in Treatment of Patients with Hypertension, J. A. M. A. **94**:1822 (June 7) 1930.

12. Palmer, R. S.; Silver, L. S., and White, P. D.: The Clinical Use of Potassium Sulphocyanate in Hypertension, New England J. Med. **201**:709 (Oct. 10) 1929.

13. Borg, J. F.: Use of Sulphocyanates in Treatment of Hypertension, Minnesota Med. **13**:281 (May) 1930.

of one investigator, it produces severe and often dangerous manifestations in the hands of another.

Two groups of patients were studied. One group was given ambulatory treatment in the outpatient department and the other group was observed while confined to bed in the hospital. The hospital group, for the most part, received its medication from one person. In the ambulatory group, only those patients were selected for study by whom, we felt, it was reasonably certain that the thiocyanate was being regularly taken as prescribed. Patients treated in the hospital were observed once or more often each day. The ambulatory patients were, in most instances, observed weekly. Both sodium and potassium salts of thiocyanate were used indiscriminately, and no record was kept of the particular salt used in individual patients. The hypotensive effect of thiocyanate in this series of seventy-four trials is reported in another paper. This study is particularly concerned with the toxic effects of the drug during its administration for therapeutic purposes.

TABLE 1.—*Summary of Data on Thirteen Patients with Essential Hypertension Who Showed Toxic Effects After Thiocyanate Administration*

Case	Group	Total Dose at Time of Thiocyanate Intoxication, Gm.	Residual Drug at Time of Thiocyanate Intoxication, Gm.	Average Daily Dose, Gm.	Duration of Medication, Days	Fall in Blood Pressure at Time of Thiocyanate Intoxication
1	Hospital	8.15	5.73	0.815	10	No
2	Hospital	11.34	.....	1.62	7	No
3	Hospital	32.54	.....	0.638	51	Yes
4	Hospital	14.49	.....	0.805	18	Yes
5	Hospital	12.71	5.00	0.978	13	No
6	Hospital	5.87	3.22	0.652	9	No
7	Hospital	26.62	21.56	1.21	22	Yes
8	Hospital	9.78	8.49	0.652	15	No
9	Hospital	14.01	.....	0.326	43	Yes
10	Ambulatory	9.13	.....	0.326	28	Yes
11	Ambulatory	11.34	.....	0.405	28	No
12	Ambulatory	17.11	.....	0.489	35	No
13	Ambulatory	11.73	.....	0.17	69	No

Table 1 represents a summary of the clinical observations in our thirteen patients who showed toxic manifestations. The ages ranged from 29 to 65, and there were eight women and five men. In all patients the hypertension was of the essential type. The average daily dose ranged from 0.17 to 1.62 Gm. The total dosage at the time of thiocyanate intoxication varied from 5.87 to 32.54 Gm. The smallest total dose given was 0.652 Gm. daily for nine days, and the largest 0.638 Gm. daily for fifty-one days. A distinct and satisfactory fall in blood pressure occurred in five of the thirteen patients. The first nine patients noted in table 1 were observed in the hospital; the last four

were ambulatory. There is noted the amount of residual thiocyanate in the body at the onset of toxic symptoms. The figure for the residual thiocyanate was arrived at by subtracting the total amount of drug excreted from the total amount administered. The quantitative determination of excretion was made on the daily twenty-four hour urine output. The procedure was to acidify 10 cc. of the urine and develop a reddish-brown to a cherry-red color with ferric chloride. The unknown was then read against a known standard in a colorimeter. While this method does admit of some inaccuracy, it is clear from table 2 that it is entirely satisfactory for supplying the information that we desired.

TABLE 2.—*Recovery of Thiocyanate in the Urine*

Diagnosis	Total Dose, Gm.	Total Thiocyanate Recovered		Recovered, per Cent
		Gm.	Days	
Chronic diffuse glomerulonephritis	10.37	7.699	30	74
Chronic diffuse glomerulonephritis	1.143	0.939	22	82
Essential hypertension	8.101	7.256	35	89.5
Normal	1.143	1.046	14	91
Normal	36.616	39.831	75	108
Normal	0.652	0.596	10	91
Normal	0.162	0.142	4	88
Normal	5.346	5.709	16	106
Normal	0.326	0.316	9	97

TABLE 3.—*Comparison of Two Methods for the Quantitative Estimation of Thiocyanate in the Urine in Man*

Ferric Chloride Method, Gm. per 100 Cc.	Schreiber's [14] Method, Gm. per 100 Cc.	Exact Amount Known to be Present, Gm. per 100 Cc.
0.0160	0.0165	0.0163
0.0080	0.0100	0.0081

It will be seen that in eight of nine trials, over 80 per cent of thiocyanate was recovered in the urine, and in five of nine trials over 90 per cent was recovered. Furthermore, a correlation of this method with the more involved method described by Schreiber [14] showed them to be strictly comparable (table 3). That thiocyanate can be quantitatively recovered in the urine was shown by Pollak,[15] who used an exact titration method.

Because of the difference in the excretion rate of thiocyanate in different individuals, it occurred to us that the total amount of drug taken up to the fall in blood pressure or the onset of thiocyanate

14. Schreiber, H.: Thiocyanate Content of Human Blood Serum, Biochem. Ztschr. **163**:241, 1925.

15. Pollak, L.: Ueber das Schicksal der Rhodanate im tierischen Organismus, Beitr. z. chem. Physiol. u. Path. **2**:430, 1902.

intoxication did not give a true account of the actual amount necessary to produce these effects. It therefore seemed necessary to make accurate and daily observations on the amount of thiocyanate taken and the amount excreted, to determine the amount of residual drug in the body at the first evidence of its effect. Accordingly, a group was selected consisting of three persons with normal blood pressure, six with essential hypertension and two with hypertension associated with chronic diffuse glomerulonephritis. The results of these observations are shown in table 4. There can be little doubt from the observations presented that toxic effects and even a fatal outcome may occur in some patients who have in their tissues a smaller amount of thiocyanate than others who not only do not become toxic but experience a satisfactory fall in

TABLE 4.—*Amount of Thiocyanate in the Body at the Time of the First Definite Fall in Blood Pressure and at the Time of the First Sign of Intoxication*

	Dosage, Gm.		Residual Drug at First Fall in Blood Pressure, Gm.	Residual Drug at Thiocyanate Intoxication, Gm.	Average Daily Thiocyanate Output in Urine, Gm.
	Total	Average Daily			
Nephritic*	9.78	0.978	8.96	.....	0.097
Nephritic*	10.80	1.080	9.03	.....	0.275
Essential hypertension	9.78	0.652	.....	8.40 (died)	0.086
Essential hypertension	12.71	0.978	.....	5.00	0.536
Essential hypertension	8.15	0.815	.....	5.73	0.213
Essential hypertension	9.78	0.978	8.09	.....	0.192
Essential hypertension	5.87	0.652	.....	3.22	0.151
Essential hypertension	26.62	1.210	20.88†	21.56	0.262
Normal	4.89	0.978	2.29	.....	0.339
Normal	4.56	0.326	2.89	.....	.....
Normal	3.26	0.652	2.90	.....	0.115

* Associated with diffuse glomerulonephritis.
† See text.

blood pressure. There is only one exception to this observation, in the one patient who exhibited signs of intoxication after the enormous amount of 21.56 Gm. of thiocyanate had accumulated in the body. It is interesting that in this patient there occurred a satisfactory fall in blood pressure seven days after the drug was discontinued and after 0.68 Gm. had been excreted. It apparently required a smaller amount of residual thiocyanate to effect a fall in normal blood pressure than when the pressure was abnormally elevated.

Of the fifty patients with hypertension in this series treated seventy-four different times with thiocyanate, thirteen presented toxic manifestations. In eleven of these the toxic manifestations disappeared within a few hours to four days after discontinuance of the drug. The usual order in which the toxic symptoms made their appearance was as follows: muscular fatigue accompanied or followed by nausea; vomiting;

disorientation and mental confusion; motor aphasia; hallucinations of sight and hearing, and, in the fatal cases, progression to delirium, convulsive twitchings, coma and death. The frequency with which these toxic manifestations were observed is shown in table 5. It is noteworthy that while ambulatory patients who become toxic notice muscle fatigue as the first indication, this symptom may pass entirely unnoticed in patients confined to bed. In these bed patients it is not unusual for motor aphasia, mental confusion or even hallucinations to be the first sign of thiocyanate intoxication.

The remaining two patients who became toxic finally died of thiocyanate poisoning in spite of drastic measures to induce elimination of the drug.

The first fatal case was that of patient M., aged 40. Her hypertension was of the essential type. The duration of her hypertension was not known. Three months before admission to the hospital she

TABLE 5.—*Frequency of Occurrence of Toxic Manifestations*

Toxic Manifestations	Frequency of Occurrence
Nausea	8
Muscular fatigue	7
Vomiting	7
Mental confusion and disorientation	7
Hallucinations of sight and hearing	6
Motor aphasia	3
Death	2
Dermatitis	1

developed a severe occipital headache, which was continuous, and dimness of vision. Her blood pressure during the control period, ranged between 255 systolic and 130 diastolic and 204 systolic and 100 diastolic. The fundi showed the classic changes of malignant hypertensive neuroretinitis. The concentration test showed a fixation of specific gravity between 1.008 and 1.014. The red blood cells numbered 4,000,000, and the hemoglobin content was 50 per cent. The urine was negative for albumin and blood. On the thirteenth day after admission thiocyanate was begun in dosage of 0.652 Gm. daily. On the fourteenth day, after 9.12 Gm. had been given, the patient complained of nausea and the blood pressure was 186 systolic and 96 diastolic. On the following day nausea was more marked, but the blood pressure had risen to 220 systolic and 110 diastolic, so that another dose of 0.652 Gm. was given. Later on this day she became somewhat confused and incoherent. Thiocyanate was discontinued. A total of 9.77 Gm. had been given in fifteen days. The blood pressure continued high, and on the following day she became violently delirious with hallucinations of sight and hearing, extreme motor restlessness, nystagmus and frequent convulsive movements of

the extremities. She was completely disorientated, continually muttering and thrashing about so violently as to require mechanical restraint. During the last twenty-four hours she voided almost no urine and was markedly dehydrated in spite of repeated saline hypodermoclyses and dextrose infusions. The stuporous state became more profound, and death occurred sixty-six hours after thiocyanate had been discontinued. On the day of death, the blood pressure was 212 systolic and 106 diastolic. Seven days before the end the nonprotein nitrogen content of the blood was 33 mg. per hundred cubic centimeters. Two days before the end the nonprotein nitrogen content was still within the normal range, being 45 mg., and the creatinine 2.4 mg. per hundred cubic centimeters. On the same day the urea clearance showed 41.2 per cent of normal function for the first hour and 34.8 per cent for the second hour. At the time of onset of the toxic symptoms, 1.29 Gm. of thiocyanate

TABLE 6.—*Analysis of Tissues for Thiocyanate Content*

Tissue	Estimation of Thiocyanate Content of Tissues of a Patient in Whom the Drug Proved Fatal,* Mg. per 100 Cc.	Estimation of Thiocyanate Content of Tissues of a Patient to Whom no Thiocyanate Was Given, Mg. per 100 Cc.
Heart	9.7	.....
Kidney	15.4	Trace
Spleen	9.2	Trace
Liver	14.5	4.0
Lung	17.0	None
Bone	None	None
Brain	8.0	None

* Patient M. (see text).

had been recovered in the urine, leaving a residual of 8.49 Gm. A necropsy was performed. The anatomic findings were: lungs, congestion; heart, pericardial effusion, hypertrophy, inactive mitral stenosis and subendocardial hemorrhages; atheroma and ulceration in the abdominal aorta; kidneys, nephrosclerosis with profound arteriolar sclerosis, but no necrotizing lesions, and predominantly normal glomeruli; brain, edema.

The fresh tissues were analyzed for thiocyanate content. Table 6 indicates the results of the analysis as compared with the tissue content in a patient who had not received the drug during life. These analyses were made by Dr. Kenneth Blanchard of the department of biology, New York University. The method used was as follows: The tissues were carefully washed free from blood. Ten gram portions of each tissue were weighed out, frozen with carbon dioxide snow and triturated with 25 cc. of water. This mixture was centrifugated and the residue washed. To the washed residue was added 50 cc. of water. To 15 cc. of the extract was added 15 cc. of trichloracetic acid; this was allowed

to stand for fifteen minutes and filtered. To 10 cc. of the filtrate was added 7.5 cc. of Schreiber's [14] reagent, and the color so developed was read against a standard thiocyanate made with 5 per cent trichloracetic acid.

The second fatal case was that of patient Mic., a woman, aged 56. Her hypertension was of the essential type. During the control period her blood pressure ranged from 220 systolic and 130 diastolic to 190 systolic and 100 diastolic. After receiving a total of 14.49 Gm. in eighteen days, an average daily dose of 0.805 Gm., she complained of nausea. The thiocyanate was immediately discontinued. There had been no appreciable fall in blood pressure. Forty-eight hours after the drug had been discontinued she developed nervous manifestations almost identical with those described in patient M. In spite of all measures to induce elimination she persisted in this state for six days and died. Two days after thiocyanate was stopped, the blood pressure fell to 158 systolic and 90 diastolic, and on the day of death, four days later, it was 90 systolic and 30 diastolic. Necropsy was not permitted.

COMMENT

Nichols [7] administered lethal doses of thiocyanate to guinea-pigs and noted a characteristic train of signs and symptoms. In the final state of poisoning he noted intense stimulation and irritation of the motor cells of the spinal cord, extreme muscular weakness, tremors and finally generalized tonic and clonic convulsions, rigidity, coma and death. Our two fatal cases in man presented manifestations entirely comparable to those described in guinea-pigs.

In an attempt to explain the occurrence of toxic phenomena, one is first concerned with the dosage used. It might be expected that toxic manifestations would occur only when the larger dosages were given. That this is not so in the case of thiocyanate is clear from table 4. Severe toxic manifestations occurred in some patients who had received less of the drug, both in total and average daily dosage, than others who developed no toxic signs. This confirms an observation by Nichols,[7] who found that some guinea-pigs succumbed to 200 mg. per kilogram of body weight, while others survived 300 mg.

Our data lead us to believe that some persons, for reasons which are not clear, show a distinct susceptibility to thiocyanate. This susceptibility manifests itself by certain symptoms of which the earliest are muscular weakness and nausea. It further appears from our observations that in certain persons there is little or no margin of safety between the toxic and therapeutically effective dosage of thiocyanate. At this time we know of no way of distinguishing those persons who will exhibit susceptibility from those in whom the drug lowers blood pressure effectively without the development of toxic symptoms.

SUMMARY

Data are presented on thirteen patients who showed toxic manifestations from thiocyanate, administered for therapeutic purposes.

Two of these patients died as a result of thiocyanate poisoning.

The incidence of toxic manifestations in this series was 17 per cent.

The frequency and order of appearance of the various toxic manifestations are noted.

A fall in blood pressure, the occurrence of toxic manifestations and death were found to be unrelated to the amount of thiocyanate administered or to the amount of residual drug in the body.

Data are presented showing that in some patients there is little or no margin of safety between the toxic and therapeutically effective dose of thiocyanate.

Tissue analysis for thiocyanate and necropsy observations are presented in one of the fatal cases.

THE EFFECT OF INSULIN THERAPY ON PANCREATIC ENZYMES IN MALNUTRITION*

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The present study was undertaken to discover whether insulin therapy, when applied to nondiabetic patients with malnutrition promotes the normal secretion of pancreatic enzymes and to prove thereby that the striking gains in weight in such a group may be attributed in part to an increased digestion and assimilation of aliment. Other investigators [1] have shown that the ingestion of the same diet without insulin produced comparatively slight increase in weight. In the recent literature on carbohydrate metabolism,[2] physiologists accept the fact that the hypoglycemia produced by the injection of insulin, and acting on the secretory and motor centers in the medulla, causes gastric and intestinal hypermotility, as well as pancreatic and biliary hypersecretion. The effect of the injection of insulin in augmenting the normal function of the tissues to hold water, carbohydrate, fat and protein is the fundamental criterion of insulin therapy and will be mentioned later in the discussion on the action of insulin. In this study the potency of the pancreatic enzymes was quantitatively measured before and after four weeks' administration of insulin. The results obtained in a group of twenty asthenic, or undernourished, nondiabetic patients, all of whom sought relief for gastro-intestinal disease or symptoms, tend to show that after the course of insulin the pancreatic enzymes exhibited uniformly an increased potency. The presence of bile rich in salts and a normal duodenal mucosa are of course essential to the normal activity of the pancreatic enzymes.

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* From the Gastro-Intestinal Clinic, Out-Patient Department, Pennsylvania Hospital.

* Read before the Thirty-Fourth Annual Meeting of the American Gastro-Enterological Association, Atlantic City, May 5, 1931.

1. Appel, K. E.; Farr, C. B., and Marshall, H. K.: Insulin in Undernutrition in the Psychoses, Arch. Neurol. & Psychiat. **21**:149 (Jan.) 1929.

2. Okada, S.; Kuramochi, K.; Tsukahara, T., and Ooinoue, T.: The Humoroneural Regulations of the Gastric, Pancreatic and Biliary Secretions, Arch. Int. Med. **43**:469 (April) 1929. Carlson, A. J.: The Extrinsic Nervous Control of the Large Bowel, J. A. M. A. **94**:78 (Jan. 11) 1930.

Twenty patients were selected and volunteered for the study. Two were not included in the survey; a test for sugar tolerance proved one patient to be a prediabetic, and the other to be hypoglycemic. The remaining eighteen were suffering from gastro-intestinal diseases or symptoms, the latter associated with other systemic diseases. The following diagnoses were made: achylia gastrica, four; pernicious anemia, three; gastroduodenal new growth, three; chronic eczema, two; giardiasis, two; visceroptosis, two; hyperthyroidism, one, and senility, one.

METHODS

The pancreatic enzymes were estimated twice prior to the four weeks' course of insulin and once or twice thereafter. The three fractions: duodenal residue (*A*), after stimulation (*B*), and later flow (*C*) were separately studied for amylase, trypsin and lipase so that as many as twelve measurements of potency of each enzyme were recorded for the same patient. The stool was examined before and after the administration of insulin to compare the degree of digestion of food elements. Estimations of blood sugar in order to insure normal or decreased curves for sugar tolerance, basal metabolism readings and Sellards' bicarbonate test of urine excreted during fasting were included in the survey.

Amylase was studied quantitatively by the Gaultier method, as modified by Lueders, Bergeim and Rehfuss;[3] trypsin and lipase were estimated as to their concentration, expressed in minutes and fractions thereof, the aforementioned methods being used, with a further most essential modification of Hollander,[4] who applied the "time law" of Hedin[5] for trypsin and lipase: "To obtain the same effect with varying amounts of an enzyme, the time of digestion must vary inversely with the concentration of enzyme." This law does not apply to amylase activity, in which the factor of reversibility is negligible and in which a direct linear proportionality exists between the amount of enzyme present and the amount of hydrolysis effected.

The aforementioned methods show only a narrow range for normal concentration of the three enzymes, and have restored a faith in the clinical value of routine pancreatic ferment studies, which all previous methods, including our own, had well nigh destroyed. The monograph, "The Nature of Enzyme Action" by Sir William M. Bayliss,[5] published in 1925, is invaluable to the student of general cellular metabolism as effected by enzymic power of decomposition and assimilation.

ADMINISTRATION OF INSULIN

I was fortunate in having the cooperation and assistance of the diabetes clinic of the Pennsylvania Hospital. It was there that the clinic

3. Lueders, C. W.; Bergeim, O., and Rehfuss, M. E.: Quantitative Determination of Enzyme Activity in Duodenal Fluids, Am. J. M. Sc. **166**:535 (Oct.) 1923.

4. Hollander, E., and Marcus, J. M.: Pancreatic Function: I. The Quantitative Determination of Pancreatic Enzymes, Arch. Int. Med. **36**:585 (Oct.) 1925. Hollander, E.: A Clinical Method for the Quantitative Determination of Pancreatic Ferments in Duodenal Contents, J. Lab. & Clin. Med. **16**:460 (Feb.) 1931.

5. Bayliss, Sir W. M.: The Nature of Enzyme Action, London, 1925.

patients were taught the use of the syringe and insulin and given a typewritten form of a schedule of administration of insulin and of a diet rich in carbohydrates and fats. This schedule followed closely that of Appel, Farr and Marshall,[1] except that to the ambulatory patients no injections were given in the middle of the day. Twenty units given twice daily was the average maximum dose for both sexes. Hypoglycemic reactions were more frequent in the women: visual symptoms, sweating and especially weakness, which disappeared within half an hour after the ingestion of sweetened orange juice, a chocolate bar or other food. The average cost for the four weeks' insulin study did not exceed $5 per patient. The insulin was purchased at hospital cost; the syringes (Lilly "Unit" graduated) were loaned on the payment of a deposit.

TABLE 1.—*Units of Insulin Administered During Experiment*

Days	Breakfast Units	Dinner Units
1	5	5
2	5	5
3 to 6th	10	10
7 to 13th	15	15
14 to 20th	20	20
21 to 27th	20	25
28 to 34th	25	30
34 to 40th	30	30

Note.—Since the body appears to become more or less insulin-resistant after the tenth day and the appetite less keen after insulin, it is advisable to step up the early doses by five units, if symptoms of hypoglycemia are relieved by frequent feedings. The greater the appetite the first ten days the more rapid the gain in weight.

SCHEDULE FOR THE ADMINISTRATION OF INSULIN

To be given from fifteen to thirty minutes before breakfast and dinner; in fleshy outer portions of arm and thighs, in rotation to prevent local inflammation; small raised itching nodules relieved by alcohol dressings.

Principles of Diet with Insulin: 1. High carbohydrate and fat diet. 2. Sugar to relieve symptoms of hypoglycemia. 3. Diet of 4,000 calories causes rapid gain. 4. Carbohydrate needs: 30 Gm. per ten units of insulin. 5. Fat meats aid in rapid gain; lean meats increase musculature throughout body.

Average full diet: farina, vegetable soup, potatoes, biscuits, oranges, oatmeal, cream, butter, eggs, toast and bread with excess butter. Add vitamin "B" rich foods; whole grain cereals, asparagus, tomatoes, beans, leafy vegetables, milk, spinach, bananas, yeast. Give extra large meat helping and extra helping of vegetables.

Give: 1. A vitamin B concentrate (Bemax), tablespoonful in orange juice or on cereal at breakfast. One glass of milk containing two teaspoonfuls of malted milk, two eggs, 1 ounce of cream and one teaspoonful of sugar mid-morning and mid-afternoon.

2. Two pieces of buttered toast and one glass of milk at bedtime.

3. Patient never to be without lump sugar or chocolate bar to take if symptoms of hypoglycemia occur.
4. Weigh patient once weekly, preferably nude.

Note: 5. Symptoms of hypoglycemia: If patient becomes weak, restless, pale, perspires, trembles, has rapid pulse, shortness of breath, vertigo or visual changes, give sugar, chocolate bar or the juice of two oranges and a teaspoonful of dextrose and call a physician.

6. To hospital patients with insulin shock from large doses, give 25 or 50 Gm. of dextrose intravenously.
7. At the most active part of the day, more food must be eaten to counteract the endogenous insulin formed.

QUANTITATIVE ESTIMATION OF ENZYME ACTIVITY

Collection of Samples.—Follow the regular Lyon technic for duodenal drainage with the following departures:

1. After extracting the gastric contents with a syringe, do not give gastric lavage.
2. Never use the syringe for the collection of duodenal samples; use only gravity return.
3. Keep the upper end of the duodenal tube open throughout the twenty minute gradual passage of the tip from the 50 cm. mark to 1 inch (2.5 cm.) beyond the 70 cm. mark.
4. If possible, avoid stimulation wi 0 cc. of hot water either to locate the tip or to relax the sphincter oddi, til after another twenty minutes. When the forefinger is placed as a support under the tube and the finger is slid away from the patient's lips, a good tug on the tube usually denotes that the tip is in the duodenum. If there is no duodenal residue, give 50 cc. of hot water and allow an immediate return, which usually effects a common duct bile (*A*) return.
5. Give a half stimulation, 37.5 cc. of a 33 per cent solution of magnesium sulphate. Wait five minutes before permitting siphonage.
6. Discard all samples that are cloudy or opaque (gastric juice), or that contain free hydrochloric acid or a total acidity of over 0.2 cc. of tenth-normal hydrochloric acid for 1 cc. of sample.
7. If the returns are cloudy, place the patient on his back until samples begin to flow clear.
8. After 10 cc. of "*B*" and "*C*" bile is collected, the drainage is completed, and the Lyon technic is resumed, with duodenal instillation of physiologic solution of sodium chloride and giving of nutriment before the patient leaves the office or clinic.
9. Collect all samples in small tubes or flasks surrounded by cracked ice in small beakers or enamel bowls. Samples of 10 cc. (crystal clear) are sufficient.
10. Place samples immediately in ice chest if enzymes cannot be estimated at once, which is the ideal method.

Amylolytic Activity.—Amylase is determined[4] by estimating the maltose formed by the action of 1 cc. of duodenal fluid on 20 cc. of a 5 per cent solution of starch made neutral or faintly pink, with phenolphthalein as indicator. (Merck's soluble starch according to Lintner was used.) Since amylase is most active on the acid side of neutrality, the slight acidity of the duodenal fluid (from 0.1 to 0.2 cc. tenth-

TABLE 2.—*Laboratory Data Before and After the Administration of Insulin*

No.	Name	Diagnosis	Sugar Tolerance F.	1 Hr.	2 Hr.	3 Hr.	Rate of Basal Metabolism	Sellards' Test,* Sodium Bicarbonate, Gm.	Blood Coagulation, Min.	Sellards' Test after Insulin, Sodium Bicarbonate, Gm.	Before Insulin: Weight	Stool	Trypsin, Min.	Lipase, Min.	Amylase Maltose, Gm.	After Insulin: Weight	Stool	Trypsin, Min.	Lipase, Min.	Amylase Maltose, Gm.
1	H. D. S.	Chronic eczema	91	141	123	96	−5	..	8	..	104	Vegetative cells; dry; fair digestion	10	+15	0.37	112½	Vegetative cells; moist; good digestion	1½ ½ 4½	3½ 3 5½	1.20 0.80 0.60
2	C. B.	Achylia; visceroptosis	90	250	225	...	....	10	..	5	82	Striated and unstriated muscle; scybalous	6 5	7 4	0.50 0.50	89¾	Moist; rare striated muscle	2½	2½	0.60
3	E. H. H.	Achylia; chronic malaria	95	102	106	119	....	10	3	5	124½	Occasional fat; occasional muscle	5 3	4½ 2	0.50 0.42	1 1	No fat; occasional muscle	1¾	3¼	0.60
4	P. M.	Achylia	95	195	113	...	. ..	..	..	..	122¾	Good digestion	3 2	2 4	0.62 0.50	130	Good digestion	2½	3¼	0.60
5	C. E.	Pernicious anemia	145	225	225	...	....	15	..	10	151¼	Not examined	2½ 3	½ 2	0.42 0.50	161¼	Occasional fat; occasional muscle	2 2¾	2½ 3	0.63 0.60
6	J. J. C.	Chronic eczema; amebiasis	135	250	160	...	....	5	7	5	154½	Scybalous; few meat fibers	3 4	12 15	0.46 0.60	167½	Moist; occasional striated muscle	1 2	4 7	0.60 0.55
7	S. R.	Achylia; gastric tumor	82	134	90	...	....	..	..	..	123	Occasional meat fiber; dry	2 4¾	7¾ 12	0.32 0.50	128½	Occasional starch; moist	3½	1½ 2½	0.37 0.37
8	T. G.	Achylia; gastric tumor	112	221	234	126	....	10	5	10	93	Excess fat; occasional meat fiber; diarrhea	4½ 4½	+20 +20	0.33 0.60	110	No fat; meat or starch formed	6 6½	5¼ 10	0.30 0.37
9	M. McG.	Scurvy (1 week of insulin)	90	187	203	183	−10	..	..	..	141½	Soft; fair digestion of starch and fat	3 8½	+20 +20	0.21 0.19	145½	Diarrhea; fair digestion	2¾	5½	0.27

10	M. S.	Giardiasis; cholecystectomy	120	172	156	98	+1	..	..	..	150	Poor digestion of all foods	3¼ 4	4 3½	0.60 0.30	153½	No change	9 4½	6¼ 3¼	0.37 0.33*
11	C. R. P.	Pernicious anemia; psychosis	121	196	129	...	−17	10	5½	10	122½	Much undigested meat fibers	4½ 6	8½ 4½	0.50 0.42	129½	Good digestion; fatty acid crystals	3 3¾	3 3	0.60 0.60
12	B. K.	Inactive tuberculosis; visceroptosis	96	150	110	...	+2	..	..	..	103½	Scybalous; fair digestion	4½ 3¾	1¼ 1½	0.42 0.42	110½	Soft; fair digestion	6¾	1½	0.37
13	E. F.	Hyperthyroid; achlorhydria	94	111	137	107	+22	..	5	..	116	Fair digestion of fat, starch and meat	3¾ 6¼	+20 +20	0.60 0.42	120¼	Firm; very occasional starch	1¾	2¾	0.42
14	E. F.	Carcinoma of stomach	83	115	54	...	....	..	..	..	119	Blood in stool; food not recorded	(Not done)			123¾	Soft; moderate muscle and starch; blood	7¾ 3	2 4¾	0.27 0.42
15	N. V.	Pernicious anemia	93 85	207	170	...	....	..	..	..	145	Slight fat and meat fibers	5½	3	0.50	150	Slight fat and meat fibers	4	2	0.42
16	M. S.	Giardiasis; cholecystitis	88	200	134	...	....	..	..	..	153	Fat and unstriated muscle	2¼ 5½	7¼ +20	0.37 0.50	164½	Soft; occasional unstriated muscle, no fat	5¼ 5¾	2½ 3½	0.42 0.42
17	C. A.	Achylia	77	121	92	...	....	..	..	..	158	Not examined	3½ 6	4 4½	0.50 0.42	171	Unstriated muscle	4¾	3	0.37
18	M. M.	Senility	92	137	91	...	....	..	..	..	105½	Neutral fat; excess starch	7½	6	0.27	112¼	Occasional starch	5½	4¾	0.37
19	P. G.	Visceroptosis	85	137	120	...	....	..	..	..	98	Scybalous; excess undigested food	2¾	4½	0.42	100	Soft; excess starch, untriated muscle, slight fat	4 7½	1½ 3½	0.42 0.39
20	S. M.	Mitral stenosis; hypoglycemia	86 77	... 88	... 93	...	−10	..	..	..	107½	Not examined	4	+30	0.33	110½	Firm; complete digestion			

* Sellards, A. W.: Acidosis, 1917. The amount of sodium bicarbonate, in 5 Gm. doses every half hour, to render fasting acid urine neutral. Sellards, A. W.: The Principles of Acidosis and Clinical Methods for Its Study, Cambridge, Harvard University Press, 1917.

normal) is sufficient to effect this condition of the substrate with loss of pink color. Incubate flasks for one hour at 37 C., shaking them every fifteen minutes. When the flasks are removed, add a small amount of sodium carbonate to stop digestion. Pour the digestion mixture into a 10 cc. buret and run slowly, then drop by drop into 5 cc. of boiling Benedict's quantitative reagent, to which has been added from 1 to 2 Gm. of sodium carbonate and a small amount of powdered talc (to prevent bubbling over). When the last blue color disappears but before the gray changes to decided pink, the end point is reached. The buret reading, divided into 0.0149 (the number of grams of maltose required to reduce 5 cc. of Benedict's reagent) gives the amount of maltose in 1 cc. of the digestion mixture. This figure is multiplied by 20 to obtain the total amount of maltose formed (table 2a).

Tryptic Activity.—For a transparent water bath, use a 2 to 4 liter pyrex beaker; fill three-fourths full of warm water, set on a high tripod above a micro-burner and maintain a temperature of from 37 to 40 C. Insert a circular copper test tube rack with holes to support six or more large test tubes with a capacity of about 50 cc., and a diameter of 1 inch. Mark three tubes: trypsin *A*, trypsin *B* and trypsin *C*. Pipet into each tube 25 cc. of a neutral 5 per cent emulsion of melted gelatin. Test

TABLE 2a.—*Conversion for Total Maltose*

Buret Reading, Cc.	Maltose, Gm.	Buret Reading, Cc.	Maltose, Gm.
0.3	0.99	1.1	0.27
0.4	0.74	1.2	0.25
0.5	0.60	1.3	0.23
0.6	0.50	1.4	0.21
0.7	0.42	1.5	0.20
0.8	0.37	1.6	0.19
0.9	0.33	1.7	0.17
1.0	0.30	1.8	0.16
		2.0	0.15

samples of duodenal fluid for acidity. Discard samples containing free hydrochloric acid or having a total acidity of over 0.2 cc. tenth-normal for 1 cc. of duodenal fluid. For correction add the identical amount of tenth-normal sodium hydrochloride to the neutral substrate in the proper test tube. Start a time clock (such as the Interval Timer of the Victor Electric Corporation). Record time in minutes and fractions as 0.5 cc. of each duodenal extraction is delivered from a 1 cc. graduated pipet into the respective *A*, *B* and *C* tubes. Remove tubes from the water bath, close the tube with the palm, shake quickly and return to the water bath. Then add 0.5 cc. of tenth-normal sodium hydroxide to each tube from a buret and shake. As soon as the dark pink changes to light add the final 5 cc. of tenth-normal sodium hydroxide. Note the exact time when the very light pink of the control or of the original emulsion or a light yellow-brown containing no pink is reached. Record the total time required for the reduction of the 1 cc. of tenth-normal sodium hydroxide in minutes and fractions.

If the time for return to neutrality is ten minutes or over, do not record results as final. Repeat the aforementioned procedure but wait three minutes after the delivery of the duodenal fluid before adding the first 0.5 cc. of tenth-normal sodium hydroxide. Through this slight change in technic a slowly active tryptic ferment has been found to fall within figures of clinical significance when previously it would have been reported as greatly delayed or completely absent.

Lipolytic Activity.—For trypsin the aforementioned procedure is used, with the following exceptions: Use only 0.1 cc. of A, B and C duodenal fluids; always

wait three minutes,[6] then add 0.5 cc. of tenth-normal sodium hydroxide; wait until the mixture completely loses its pink color before adding the final 0.5 cc. of tenth-normal sodium hydroxide. Record exactly the time of adding the duodenal juice, and the time when the mixture with the added 1 cc. of tenth-normal sodium hydroxide has lost every trace of pink color or returned to its original neutrality. If in ten minutes the result is negative, repeat the test, but use 0.5 cc. of duodenal fluid. Multiply the time figures by 5.

Time figures of five minutes or less for the formed amino acids and fatty acids to neutralize 1 cc. of tenth-normal sodium hydroxide are considered normal concentrations of tryptic and lipolytic enzymes, respectively.

Five Per Cent Starch Solution.—Stir 25 Gm. of Merck's soluble starch (Lintner) into a smooth paste in a mortar by adding slowly 30 cc. of cold distilled

TABLE 3.—*Enzyme Concentration in Five Cases of Diabetes*

	Trypsin			Lipase			Amylase		
	A	B	C	A	B	C	A	B	C
Case	Minutes			Minutes			Gm. of Maltose		
1	9	20+	14¼	4¼	6	4¼	0.27	0.14	0.23
2	20	12	0	16¼	10¼	30	0.15	0.19	0.00
3	40	0	20	27½	12	4½	0.30	0.15	0.25
4	3¾	5½	13	4½	4½	4½	0.35	0.25	0.27
5	10	15	12	3½	3½	3½	0.35	0.23	0.21

TABLE 4.—*Enzyme Concentration in Patients of Normal Weight*

	Trypsin			Lipase			Amylase		
	A	B	C	A	B	C	A	B	C
Diagnosis	Minutes			Minutes			Gm. of Maltose		
Giardiasis	7	5	5¼	3½	—3	—3	0.42	0.42	0.37
Gallbladder adhesions	0	9¾	5¼	0	—3	—3	0.40	0.19	0.30
Hypochlorhydria	9½	7	7¼	3¼	—3	—3	0.37	0.42	0.37
Hyperchlorhydria	4½	4½	4¼	—3	—3	—3	0.37	0.23	0.15
Hypochlorhydria; gallbladder adhesions	0	7	12	4¼	3	3¼	0.40	0.27	0.30
Gallbladder stasis	..	6½	..	4½	—3	—3	0.30	0.27	0.27

water. Heat to boiling 470 cc. of distilled water in a 500 cc. pyrex sterile flask. Pour gradually into starch paste, stirring continuously to insure a mixture free from lumps. Pour the solution back into the warm pyrex flask. Add toluene to cover the starch solution with a ¼ inch layer. Keep at room temperature. Shake well before using.

6. Lipase is more sensitive to tenth-normal sodium hydroxide than is trypsin. When amounts as low as 0.1 cc. of duodenal juice are used, one can conceive of a dilution of ferment so great that 1 cc. of tenth-normal sodium hydroxide might disturb its activity, or even destroy it. The three minute wait permits the ferment to act in a neutral mixture or weakly acid one (formed fatty acids). Though many duodenal fluids have an active lipolytic ferment in high concentration, even in only 0.1 cc. of the digestive fluid, later experience may bring a further modification in the technic, namely, the use of 0.5 cc. of duodenal juice for both tryptic and lipolytic activity.

Five Per Cent Emulsion of Gelatin.—Dissolve 25 Gm. of Bacto-gelatin in 300 cc. of distilled water in a 500 cc. pyrex flask set in a water bath. Raise the temperature gradually until the gelatin is perfectly dissolved and clear. In a mortar place 12.5 Gm. of acacia, U.S.P. (purest grade), add gradually 50 cc. of liquid petrolatum, rub into a smooth paste, then add all at once 25 cc. of distilled water, and continue stirring in one direction until a milk white emulsion is formed. To this add the 300 cc. of melted gelatin. Pour into a graduated cylinder. Make up to 500 cc. with washings of mortar and warm distilled water. Pour into a 500 cc. sterile flask, add 3 cc. of a 1 per cent alcoholic solution of phenolphthalein and make neutral (faint pink) with normal sodium hydroxide. Shake well, then distribute into storage flasks. Cover the emulsion in flasks with a thin layer of toluene; store in the ice chest. When needed liquefy by gentle heat in a water bath (a temperature of 60 C. will scorch gelatin). Shake well to insure an even emulsion before measuring into test tubes.

Olive Oil Emulsion (20 Per Cent).—Place 25 Gm. of acacia (purest grade) in a mortar, add gradually 100 cc. of highest quality olive oil; rub into a smooth paste; then add all at once 50 cc. of distilled water, and continue stirring in one direction until a milk white emulsion is formed. Add more distilled water; make up to 500 cc. in a graduated cylinder, using washings of mortar with distilled water. Pour into a 500 cc. flask. Add 3 cc. of phenolphthalein and sufficient normal sodium hydroxide (about 1.5 cc.) to make neutral or faint pink. Shake well to insure an even emulsion before pipetting into test tubes.

After considerable experiment it was found that dependable results were obtained only with freshly prepared oil emulsion. Formaldehyde as a preservative was not satisfactory; toluene with the oil emulsion gave larger figures for time or negative results. Sterilization also proved unsatisfactory. Further experimentation on this problem is being continued.

THE INSULIN SYSTEM

In their latest investigations, Depisch and Hasenöhrl [7] arrive at the following conclusions:

> The assimilatory insulin system with its nervous regulation stands in the center of the carbohydrate metabolism. It promotes the absorption of sugar both in the liver and the tissues. In the liver this system is counteracted by the sympathetic nervous system and the secretion of the suprarenals, of the posterior lobe of the hypophysis, and of the thyroid (liver counter-regulation). In the tissues the effect of insulin is counteracted by the suprarenals and the thyroid: (tissue counter-regulation). Independent of this hormonal regulation there appears to be also a direct influence of the nervous system on the sugar metabolism in the liver and tissues both promoting and checking it.

The glycogen-insulin mechanism is shown by Okada [8] to be vital in the physiologic process of oxidation, as an incessant oxidation of sugar is unconditionally necessary to maintain the living process. The regulatory influence of this active sugar on the function of the digestive tissues is similar to that of oxygen on the function of the respiratory organs. A deficiency either of oxygen or sugar stimulates the vagus

7. Depisch, F., and Hasenöhrl, R.: Klin. Wchnschr. **9**:345, 1930.

8. Okada, S., et al.: Pancreatic Function: V. The Secretory Mechanism of the Digestive Juices, Arch. Int. Med. **45**:783 (May) 1930.

centers, lack of oxygen producing forced respiration, hypoglycemia, digestive hypersecretion, especially of pancreatic juice and bile, as well as hypermotility of the digestive tract.

The pancreas, the source of insulin, is the most important organ in the carbohydrate metabolism of the body. The external as well as the internal secretion plays a rôle of prime importance. According to Boldyreff,[9] the uncombined pancreatic ferments are reabsorbed from the intestines into the blood and find their way to all tissues in the body. Their presence is required to explain many of the vital processes of a biochemical character in the cells and the tissues. Fischer[10] also said: "Ferments or enzymes . . . their participation is established in many, more exactly investigated, biological processes, and on that account we can with sufficient probability admit that they act in all vital processes of the body." Therefore the pancreas, with the aid of the intestinal juices and bile, not only provides the enzymes for the complete digestion of food in the alimentary canal, but likewise may prove to be the source of the cellular ferments that are indispensable not only for the general metabolism of the body as a whole, but for each particular cell's power of autolysis and synthesis, as well as digestion and assimilation of nutriment.

THE ACTION OF INSULIN

On Body Tissues.—Most writers stress the retention of water along with the storage of glycogen in the cellular protoplasm and preceding the formation and storage of fat. Insulin activates the process of carbohydrate combustion in the tissues. The end-products of fat digestion cannot be fully utilized without the presence of such combustion. Oxygenation in the tissues cannot take place unless an adequate amount of dextrose is present. Meyer[11] pointed out that insulin accelerates carbohydrate metabolism by supplying an intermediary metabolism, namely, a capacity for depositing water in the cellular tissues. Feissly[12] attributes the retention of water to the increased hydrogen ion concentration of the plasma during the treatment with insulin; others, the need for water to effect carbohydrate storage. Vogt[13] stated that under the influence of insulin, respiratory tests show increased carbohydrate metabolism and an increase of the fat formation from carbohydrates.

9. Boldyreff, W. N.: The Periodical Activity of the Organism and Its Physiological and Clinical Significance, Read at Staff Meeting, Battle Creek Sanitarium, Feb., 1925.

10. Fischer, E.: Organische Syntheses und Biologie, Berlin, 1908, p. 24.

11. Meyer, L. F., and Bamberg, K.: Recurrent Acetonemic Vomiting of Children, and Its Treatment with Insulin, Deutsche med. Wchnschr. **51**:1100 (July) 1925.

12. Feissly, R.: Traitement insulinique des états de dénutrition chez les sujets non diabétiques, Presse méd. **13**:196, 1926.

13. Vogt, E.: The Insulin Treatment of Nondiabetic Affections, Med. Klin. **23**:169 (Sept. 30) 1927.

The effect on hydrogen metabolism in water-impoverished states, as in tuberculosis, is a fortunate secondary effect. The action of insulin is not a chemical one, because if the insulin is mixed with blood no glycolysis takes place. This is the reverse of the action of the external secretion of the pancreas, which reduces blood sugar probably through the action of a glycolytic enzyme.[9] All investigations on the action of insulin prove that a disturbance of carbohydrate metabolism is the result of a diminished glycolysis rather than a consequence of increased glycogenesis. The chief action of insulin is, in fact, on the tissues and liver, so affecting them that in the presence of an excess of water and oxygen glycogen is synthesized and stored.

On Pancreatic Ferments.—In their study, in 1929[2] of the humoral regulation of the gastric, pancreatic and biliary secretions, Okada and his associates definitely showed that the increased secretion of these juices, with increase of ferments and their activators, following the injection of insulin is marked in the presence of hypoglycemia, while it is nearly negative in the absence of hypoglycemia. Carusi[14] found certain signs of a functional correlated action between the two pancreatic secretions, but could not assert that there exists a functional parallel action between the internal and the external secretions. He referred to the work of Monteleone, Kahn, Jones and Cammidge as separately finding a marked decrease in the activity of pancreatic ferment in diabetes and of Monteleone's use of insulin causing a considerable increase of enzymatic activity. Lambert and Hermann found in animals with fistula of the Wirsung canal no increase in the external secretion following an injection of insulin, probably because a hypoglycemia was not established. Insulin cannot be expected to stimulate external secretion in a pancreas with histologic alterations in its acinous part.

HUMORO-NEURAL FACTORS THAT GOVERN EXTERNAL PANCREATIC SECRETION

Gayet[15] examined the secretions produced by electric stimuli applied to the pancreatic gland or to the vagus and also studied the secretions produced by secretin, injected either into the blood or into the duodenum. When direct electric stimulation was used, there was a prompt increase in the outflow of blood from the gland, which rapidly reached its maximum and which returned to the original level after the stimulation was discontinued. The flow of pancreatic juice followed an almost parallel course, but its onset and maximum were slightly retarded.

14. Carusi, R.: Concerning Pancreatic Secretions, Policlin. Roma (sez. med.) **37**:90 (Feb.) 1930.

15. Gayet, R., and Guillaumie, M.: The Reciprocal Quantitative Relations of the Secretion of Pancreatic Juice and Blood Stream, Compt. rend. Soc. de biol. **103**:1216, 1930.

When the pancreatic juice was stimulated with secretin, the output of the blood and the flow of juice were practically parallel, though the flow of juice persisted longer than the temporary increase in the outflow of blood. The increase in the flow of blood and of pancreatic juice showed the same reciprocal ratio after stimulation of the vagus. When atropine is injected into the saphenous vein the secretory response to direct stimulation of the gland is greatly decreased. Atropine had a more prolonged effect in decreasing the outflow of blood from the gland. Stimulation of the gland or vagus is affected through direct action of vasodilator nerve fibers. Hormone stimulation with secretin is explained by the theory of Bancroft, which concerns a local process determined by metabolites.

Physiologists who have studied the action of insulin in relation to blood reaction agree that this hormone, through its function of activating hydrogen, carbohydrate and fat metabolism, does aid in maintaining acid-base equilibrium and a high blood alkali reserve. Arschawsky [16] studied the influence of the change in the reaction of the blood on the secretion of the pancreas and concluded:

1. An increase of the p_H and CO_2 values of the blood enhances the stimulating effect of HCl on the secretion of the pancreas. 2. The stimulating effect of secretin upon pancreatic secretion is enhanced by an increase of p_H and CO_2 values of the blood. 3. A decrease of the normal p_H and CO_2 values of the blood inhibits the stimulating effect of HCl on external pancreatic secretion, but not that of secretin. 4. A change in the p_H and CO_2 of the blood is accompanied by a change in the CO_2 content alone, of the pancreatic juice.

Rosenkow [17] reported his results with pilocarpine and secretin before and after vagotomy. Pilocarpine has a stimulating influence on the vagal terminals. Pilocarpine becomes ineffective following vagotomy, whereas secretin stimulates effectively pancreatic secretion. In normal animals, secretin stimulates the secretion of an inactive pancreatic juice, but after vagotomy the secretion is able to split proteins (tryptic activity). The morphologic changes in the pancreas following vagotomy are expressed in an enlargement of the secretory granules and a decrease in their number, the protoplasm of the glands containing numbers of vacuoles and large secretory droplets. Therefore, the amount of pancreatic juice depends on the number of granules in the gland cells; a decrease of secretory activity is accompanied by a decrease or disappearance of granules. Rosenkow expressed the belief that pilocarpine becomes ineffective as a secretagogue after vagotomy, not because it is no longer able to act on the nerve terminals, but because it exerts a toxic action on the gland cells themselves. When the neural stimulation to secretory activity is destroyed by vagotomy, the humoral stimulant, secretin, appeared to have

16. Arschawsky, J. A.: The Influence of the Change in Blood Reaction on the Secretion of the Pancreas, Arch. f. d. ges. Physiol. **224**:128, 1930.

17. Rosenkow, I. P.: Effect of Vagotomy on Secretory Activity of the Pancreas, Arch. f. d. ges. Physiol. **223**:146, 1929.

a more potent effect in that the pancreatic juice previously inactive possessed tryptic activity. It is now recognized that the pancreas can secrete a proteolytic ferment, trypsin, as well as its precursor, trypsinogen. Rosenkow concluded that after vagotomy this activation is especially enhanced by the great enlargement of the secretory granules, even though decreased in number. Therefore, the vagi can be said to exert on the gland cells of the pancreas a trophic influence, by maintaining a definite equilibrium in the metabolism of the cells.

CONCLUSIONS

1. Injections of insulin twice daily to the average total amount of 40 units produced in a selected group of eighteen patients with malnutrition a definite, measurable increase in the concentration of pancreatic ferments recovered from the duodenum during fasting.

2. Accompaning this effect, there appeared in a number of the patients a return to a normal sequence of so-called A, B, C bile fractions; in other words, the function of the biliary tract, together with external pancreatic functions, was improved.

3. The methods employed in the estimation of enzyme concentration satisfy the essential laws of enzyme action, besides confining normal figures within narrow limits, and thus making a sharp division between high and low concentration, especially of trypsin and lipase.

4. Tests for blood sugar tolerance are required to eliminate patients with hypoglycemia as unsafe for insulin therapy in malnutrition.

5. Studies of the stool before and following insulin therapy gave results that showed a direct parallel between the more complete digestion and assimilation of food elements and the increased concentration of pancreatic ferments.

6. The aforementioned findings appear to the authors as justifiable proof that the cause of the striking gain in weight in most of the eighteen patients receiving insulin therapy was due in part to the stimulating effect of insulin on external pancreatic secretion and bile and in part to a resulting normal digestion and assimilation of aliment.

Miss S. A. Lehmann, R.N., collected the duodenal fractions and made the basal metabolism studies; Miss J. L. Yates, dietitian of the outpatient department, taught the clinic patients the use of the syringe and the insulin, and gave individual instruction as to diet and relief from hypoglycemic symptoms and prepared the printed slips containing the diet and the measures for symptomatic relief; Miss Mildred Carlisle, pharmacist, gave her assistance in the preparation of the substrates, and the laboratory technician, Miss M. E. Watson, co-author of this paper, made hundreds of estimations of pancreatic enzymes before she was satisfied that the technic was reliable.

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Book Reviews

The Treatment of Asthma. By A. H. Douthwaite, M.D., F.R.C.P. (Lond.). Price, $2.50. Pp. 160. New York: William Wood & Company, 1930.

In a small book of 160 pages the author attempts an up-to-date discussion of the diagnosis and treatment of the asthmatic patient. The material presented is fairly well handled, but the arrangement allows much repetition. The book is divided into two parts, the first dealing with theoretical, clinical and laboratory aspects of asthma and the second with therapeutics. The bibliography indicates that European literature has been the chief source of reference. The classification of asthmatic patients into primary and secondary groups depending on the age of onset and certain biochemical differences does not clarify or simplify the problem. The discussion of clinical features and pathology is very brief and elementary. As emphasized by the author, some of the metabolic and bacteriologic findings that are given must be corroborated before being accepted as significant. The following chief etiologic factors that produce attacks are discussed: allergens, local irritants, reflex stimulation, psychic influences and endocrine excitants. In the chapter on "Preliminary Investigations," proper emphasis is placed on the necessity of a complete study.

The second part of the book is devoted to a discussion of most of the modern forms of treatment. The uses and limitations of these forms of treatment are discussed. Special emphasis is placed on the value of physical therapy and on the administration of vaccine.

In the concluding chapter, the following apt paragraphs are given:

"Elimination of focal sepsis and suspected sources of reflex vagal stimulation seldom produces striking results."

"The majority of drugs are of use merely to hold symptoms in check and have no value in eliminating or correcting the asthmatic tendency."

"In no other disease is greater concentration on detail demanded of the physician. In no other illness are we so often disappointed when victory seems to be ours. Yet when we look back on the fruit of the labours of the past twenty years we cannot but be impressed by the material advance which has been made towards the ultimate conquest of this mysterious malady."

The Practice of Medicine. By A. A. Stevens. Third edition. Cloth. Price, $8. net. Pp. 1150, with illustrations. Philadelphia: W. B. Saunders Company, 1931.

The new edition of Stevens' "Practice of Medicine," while retaining the briefer one volume form of previous editions as compared to the more bulky systems, and adhering to the general form of presentation made familiar by Osler's single volume textbook, has been thoroughly deleted of all work not in accord with modern conceptions of medicine and has been brought thoroughly up to date.

In the broader subjects, such as pneumonia and typhoid, extensive revisions and additions have been made, giving a thorough contemporary presentation of those subjects. A great many sections have been completely rewritten, including those on such diseases as icterus, ulcerative colitis, agranulocytic angina, nephrosis,

the anemias, coronary occlusion and undulant fever, to mention a few representative cases. New subjects include psittacosis, toxoid prophylaxis of diphtheria, immunization to measles, antitoxin in erysipelas, parathyroid dysfunction and others of equal interest.

The subject matter is divided under the headings of infectious diseases, intoxications, deficiency diseases, disorders of metabolism and diseases according to the systems: digestive, respiratory, circulatory, renal, blood-forming, spleen, ductless glands, joints and bones, muscles and nervous system. Each topic is then dealt with in the orthodox manner, giving first a descriptive definition; historical data; etiology, including specific and predisposing factors; morbid anatomy; symptoms; signs; complications, and therapy.

The work appeals as a strictly modern, conservative and carefully planned and executed handbook for both students and physicians. All material is quickly accessible, and there is no evidence that the restriction to one volume makes it in any way limited in its scope.

A Clinical Study of Addison's Disease. By Leonard G. Rowntree, M.D., and Albert M. Snell, M.D. Cloth. Price, $4, net. Pp. 317, with 41 illustrations. Philadelphia: W. B. Saunders Company, 1931.

From a group of "approximately 300 cases in which a diagnosis of Addison's Disease (definite or tentative) had been made during life, or extensive lesions of the suprarenal gland have been found at necropsy," records of 108 patients have been selected and form the basis for this presentation.

While one is not convinced from the case reports that the diagnosis is indisputable in each instance, the authors have had a most unusual opportunity to study and treat this rare malady. Their compilation is particularly fortunate at this time, now that Swingle and Pfiffner and others have isolated a cortical hormone which gives every promise of as much ultimate success in the treatment for Addison's disease as insulin has had in the treatment for diabetes mellitus.

The history of the development of knowledge of Addison's disease before the classic description of Addison (which is reprinted in full) and the modern conceptions comprise the early chapters. Then follow the presentation of necropsy material, case reports, chapters on signs and symptoms, laboratory data, diagnosis, complications, prognosis, treatment, including the recent results in a few cases in which the patients were treated with the cortical hormone of Swingle and Pfiffner, and finally a short chapter on "statistical considerations." An excellent bibliography and index are appended.

This monograph should be in the library of every physician.

Les malades dits imaginaires. By M. Nathan. Price, 14 francs. Pp. 134. Paris: Gaston Doin, 1931.

In this short monograph, one of a series on practical medicine, the author discusses the diagnosis and treatment of so-called imaginary illnesses from a critical point of view. He first points out the dangers of such a diagnosis, giving examples of conditions that in the past were considered as functional and are now known to have an organic basis. The necessity for thorough examination for evidences of organic disease is stressed. In subsequent chapters he discusses the various forms of functional diseases and the possible associated organic conditions. The last chapter is devoted to a very brief discussion of therapy in which the author stresses the point that the type of therapy must vary with the type of case.

The book is obviously intended only as a brief and rather superficial survey of the subject matter and seems to fulfil these qualifications.